



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Safe re-entry for workers into plant protection product treated crops

RIVM Letter report 2018-0005
M. Markantonis | J.D te Biesebeek | C. Graven



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Colophon

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Synopsis

Plant protection products: Safe work into plant protection product treated crops

Workers are exposed to plant protection products (PPPs) when they enter treated crops for crop treatment, harvest or crop inspections. Before a plant protection product is authorized for sell and use, a safety assessment has to be performed. Commissioned by the ministry of SZW (Dutch Ministry of Social Affairs and Employment) RIVM has provided information to answer three itself independent questions which all relate to worker PPPs safety assessment.

RIVM developed a methodology to calculate product-specific personal protective equipment required interval for workers entering pesticide-sprayed crops. Currently for workers gloves can be prescribed on the label of a PPP. However there is no information on the label about the duration of the obligatory use of gloves. In most cases a general period of twee weeks is used, the new methodology provides a way to refine the two week period. RIVM recommends to include the period into the EU harmonised method for worker exposure estimation, the period can then be set on the label of national authorised PPP.

RIVM proposes a protocol to investigate the dermal absorption of dried residue which was available in the scientific literature. To assess if crops can be handled safely, dermal absorption absorption of dried residue is required. Currently dermal absorption is investigated with fluids. Before the protocol can be used internationally, it should be approved by the Organisation for Economic Co-operation and Development (OECD). RIVM therefore recommends to further investigate whether this protocol can be submitted for OECD approval.

Chemical substances can be classified based on their properties: for example a notification for health hazard. A substance can cause irritation of the skin or eyes or can cause allergic reactions. This is also applicable substances in PPPs. PPPs are used and sprayed diluted. For safety of workers it is therefore of importance to know the hazardous properties of the diluted PPP and it's dried foliar residue. RIVM recommends to test the hazardous properties of some diluted PPPs and it's dried foliar residue.

Keywords: plant protection products, pesticides, workers, re-entry, gloves

Publiekssamenvatting

Gewasbeschermingsmiddelen: veilig werken met behandelde gewassen

Werknemers komen in aanraking met gewasbeschermingsmiddelen wanneer ze gewassen die daarmee zijn behandeld, verzorgen, inspecteren of oogsten. Voordat een gewasbeschermingsmiddel wordt toegelaten voor verkoop en gebruik wordt daarom beoordeeld of dit veilig is. In opdracht van het Ministerie van Sociale Zaken en Werkgelegenheid heeft het RIVM drie vragen rondom deze veiligheidsbeoordeling beantwoord.

Het RIVM heeft een methode ontwikkeld om te berekenen tot hoeveel dagen nadat een gewas is behandeld een werknemer handschoenen moet dragen. Momenteel kan op het etiket van het middel staan dat het verplicht is om handschoenen te dragen, maar staat er niet bij voor hoe lang dat nodig is. Meestal wordt een algemene periode van twee weken aangehouden, maar met de nieuwe methode kan dat preciezer worden aangegeven. RIVM beveelt aan om de berekening toe te voegen aan de in Europa gangbare methode voor het bepalen van werknemer blootstelling, zodat deze periode op het etiket van in Nederland toegelaten gewasbeschermingsmiddelen kan worden aangegeven.

Het RIVM beschrijft in dit rapport een methode uit de literatuur om de opname van droge restanten via de huid te bepalen. Om te bepalen wanneer een gewas veilig kan worden aangeraakt is het belangrijk de opname via de huid van gedroogde restanten van bestrijdingsmiddelen te kunnen bepalen. Momenteel wordt op basis van opname van het vloeibare middel de veiligheid beoordeeld. Voordat deze methode internationaal kan worden gebruikt moet de Organisatie voor Economische Samenwerking en Ontwikkeling (OESO) deze methode accepteren. Het RIVM adviseert daarom om te onderzoeken hoe deze methode hiervoor in aanmerking kan komen.

Chemische stoffen worden geclassificeerd op basis van eigenschappen: bijvoorbeeld een aanduiding van het mogelijke gevaar voor de gezondheid. Zo kan een stof irritatie veroorzaken bij contact met de huid of allergische reacties veroorzaken. Dit geldt ook voor de stoffen die in gewasbeschermingsmiddelen zitten. Deze middelen worden in verdunde vorm gebruikt. Voor de veiligheid van de werknemers is het van belang om te weten of het verdunde middel en de gedroogde resten op planten nog schadelijke eigenschappen bezitten. Hierover heeft het RIVM geen gegevens kunnen vinden in de literatuur. Daarom adviseert het RIVM om te testen of spuitverdundingen van enkele middelen en de droge restanten daarvan nog schadelijke eigenschappen bezitten.

Kernwoorden: gewasbeschermingsmiddelen, pesticiden, werknemers, herbetreding, handschoenen

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Glossary

a.s	active substance
AChE	Acetylcholinesterase
AOEL	Acceptable Operator Exposure Level
AR	Applicate Rate
BHT	Butylated HydroxyToluene
BW	Body Weight
ChE	ChlorinEsterase
CLP	Classification, Labelling and Packaging
Ctgb	Dutch Board for the Authorisation of Plant Protection Products and Biocides (College voor de toelating van gewasbeschermingsmiddelen en biociden)
DA	Dermal Absorption
DAR	Draft Assessment Report
DAT	Day After Treatment
DFR	Dislodgeable Foliar Residue
Dil.	In-use working dilution of the PPP
DT50	Dissipation Time where 50% of the dissipation is reached
EC	European Commission
EFSA	European Food Safety Authority
HSE	Health, Safety & Executive
HTB	Authorization Handbook (Handboek toelating en beoordeling)
LD50	Dose where 50 % lethality is reached
MAF	Multiple Application Factor
OECD	Organisation for Economic Co-operation and Development
PDE	Potential dermal exposure (external)
PHI	Post Harvest Interval
PIE	Potential Inhalation Exposure
PPE	Personal Protective Equipment
PPERI	Personal Protective Equipment Required Interval
PPP	Plant Protection Product
REI	Re-Entry Time/ Interval
RVNAS	Reference Value for Non-acute Active Substances
SEWd	Systemic dermal Exposure Worker
SZW	Dutch Ministry of Social Affairs and Employment
T	Task duration
TC	(Dermal) Transfer Coefficient
TSE	Total Systemic Exposure
U.S.EPA	U.S. Environmental Protection Agency

Summary

In the process of legal authorization of plant protection products (PPP), the risk for the worker who re-enters the crop after treatment, for example to harvest or to do inspections of crops, is estimated by the competent authority. In general, exposure is calculated using modelling techniques, using default values amongst others. The applicant has also the possibility to provide studies (exposure studies, foliar residue decline studies and/or dermal absorption studies) for the to be-authorized plant protection product, which allow an adjustment of default values. If there is an exceedance of the toxicological reference value, it will be determined if gloves can reduce the risk sufficiently (Ctgb evaluation manual, Ctgb 2017). If this is possible the plant protection can be authorised for the aspect worker safety. If gloves are necessary this should be indicated on the label of the plant protection product (which allows a safe re-entry of the worker into the crop). The period of time for which workers must wear gloves is presently not determined or legally required. But several associated parties give advice on this area. There is however currently no EU harmonised methodology how to calculate the time period for which gloves are required to safely re-enter a treated crop.

It is also unknown if dermal absorption of dry residue (to which workers are typically exposed) is any different from wet residue, which is currently used in the risk assessment.

Furthermore, it is unclear whether specific properties of an undiluted product, such as acute toxicity, irritation or sensibilization, also apply to spray dilution.

To fill these gaps of knowledge, a methodology was developed to calculate product-specific Personal Protective Equipment Required Interval (PPERI) for workers entering pesticide-sprayed crops after typical (multiple) spray application with plant protection products (PPP). Selected PPPs authorised for agricultural use in the Netherlands served as case study and demonstrated the proof of principle and applicability. PPERI-calculations were performed for PPPs which required a refinement because the EFSA OPEX model exposure assessment resulted in an unacceptable risk for workers without the use of gloves.

The current scientific position on dermal absorption of dried residue was summarized and a new dermal absorption test protocol for dried residues was described. It was concluded that currently additional research and harmonization is required on a European level to refine the worker exposure assessment with dermal absorption studies on dried residue.

Finally, a literature search was performed to investigate whether specific properties of PPPs (e.g. acute toxicity, skin irritation and sensibilization) also apply for the spray dilutions. However specific studies presenting acute toxicity, skin irritation and sensibilization properties of the spray dilutions and/or dried residues of PPPs are not found, and therefore the

answer to this research questions remains inconclusive. The regulation on classification, labelling and packaging of substances and mixtures (CLP) can provide hazard information about a spray dilution using calculation rules, also taking into account the information of all substances in the product. The CLP regulation, however, cannot be used to define chemical properties of the dried foliar residue of the PPPs.

1 Introduction

Workers (i.e. crop workers, gardeners and flower farm workers) are potentially exposed to pesticide residues when entering pesticide-treated fields to perform a variety of hand-labor tasks, such as pruning, thinning, scouting and harvesting, required for the commercial production of agricultural crops. These types of exposures during re-entry can occur in different crops throughout the growing season and can be of similar magnitude to exposures of operators who mix, load and apply pesticides during first entry (after application when the crop is dry¹). This type of entry into crops by workers after application of a pesticide is called re-entry. The competent authority, in the Netherlands the Ctgb, must grant an authorization for a plant protection product (PPP), before the product is placed and sold at the Dutch market. For the authorization, Risk assessments (RA) must be carried out for the worker (among other human exposure scenario's e.g. operators, residents and bystanders). The expected exposure scenario for workers to be assessed depends on the proposed PPP uses (e.g. type of spray application, type of crop and type of hand-labor task). An authorization can only be granted if there is no risk from exposure to PPP, e.g. for workers wearing arm- and leg-covering normal work clothing. If risks for the worker, wearing work clothing, occur from exposure to PPP during re-entry of crops, then these risks can be mitigated by wearing gloves. Re-entry is defined in this report as the event when workers enter crop, perform first crop-related tasks after the drying period of prior sprayed PPP elapsed (a default of 2 hours drying is assumed). Wearing gloves for exposure mitigation may contradict with some hand-labor tasks, such as pruning, thinning and harvesting are delicate tasks which require a sensitive touch of the crop. A worker will therefore preferably not use gloves, or use gloves for the shortest possible time. The required time to use gloves for the safe performance of re-entry tasks is not determined during the authorization assessment. Societal parties in their information to users often mention that a period of 14 days for which gloves should be used after the application of the PPP is noted (a list of products with advised re-entry instructions can be found on www.fytostat.nl). There is currently no EU harmonized methodology available to determine the exact period for which gloves should be used after application of PPPs. A methodology to determine the period for which gloves should be used for safe re-entry time or interval (PPEI) will provide farmers with guidance to instruct the crop workers with respect exposure mitigation/avoidance as an important part of occupational safety.

To assess the risk of PPPs for the worker exposure, among other values, dermal absorption is used in the calculations. The dermal route is the primary route of exposure for the worker re-entry scenario. Dermal absorption, the process by which a substance is transported across the skin and taken up into the worker's body, is a complex process

¹ The risk assessment of workers re-entering treated crops is among other values based on the foliar residue level available directly after application when the crop is dry (EFSA, 2014).

influenced by several factors. Currently, the dermal absorption factors used in risk assessment for worker re-entry for the authorization of PPPs are the same as for the operator risk assessment. Operators are in most cases exposed to the formulation as sold (during mixing/loading) and a liquid spray dilution of the PPP. PPPs for professionals are almost always sold in a concentrated formulation which is diluted before application. A worker is in most cases exposed to the dried foliar residue of a PPP. It is questionable if the studies used for the operator exposure risk assessment are representative for the worker scenario. In general it is assumed that dried residues will penetrate the skin less efficiently compared to liquids (liquid formulation and spray dilutions). The current practice during risk assessment is a precautionary principle, using the higher dermal absorption value (usually of the in-use dilution) as no measured values for dried residues after application of dilutions are available. In future, dermal absorption values based on studies with dried residues can provide a more realistic exposure assessment. There are currently no harmonized testing protocols available for dermal absorption studies with dried residue.

As aforementioned, workers are exposed to foliar residue of PPP which is in most cases dried foliar residue. Active substances (a.s.) and PPPs can have toxic properties (e.g. acute toxic, irritation and sensibilization) that are assessed by acute toxicity studies and irritation and sensibilization studies. Based on these studies, both the a.s. in PPPs and the PPP itself, can be classified following the CLP (Classification, Labelling and Packaging) assessment. However, to date it is unclear if the hazard classifications for acute toxicity, irritation or sensibilization apply also for the spray dilution of the product or its dried foliar residue. Note: the systemic toxic properties, e.g. carcinogenicity or reproduction toxicity, is already assessed for the workers as a default assessment in the authorization procedure of a plant protection product.

1.1 Formulation of question

The Ministry of SZW (Dutch Ministry of Social Affairs and Employment projects) has requested the RIVM to provide information to answer the following in itself independent questions which all relate to worker PPP exposure and risk.

1. Provide a methodology to determine the period to enter a PPP-treated crop with gloves for a safe re-entry. Calculate the period to safely re-enter crops (PPERI) with gloves for authorized plant protection products.
2. What is the current view on dermal absorption of dry substances, i.e. worker exposure during re-entry and how relevant is this for approval of PPP's worker scenario?
3. a) Do the spray dilutions of products with toxicological properties like acute toxicity, skin irritation and or sensibilization, keep their properties and for which period?
 - a. b) Do the foliar residues of products with toxicological properties like acute toxicity, skin irritation and or sensibilization, keep their properties and for which period?

1.2 Approach

Methodology to calculate the PPERI

The RIVM proposes a mathematical algorithm to calculate a period of safe re-entry into prior sprayed crops, after which a workers can perform crop related tasks without additional protection of gloves (i.e. PPERI is a period for which gloves should be worn for a safe re-entry). The calculation method originates from the EFSA OPEX model expanded by an algorithm of the US EPA OPED model, taking into account the foliar dissipation of the active substance and multiple application of the PPP.

At first, the methodology is presented, how current worker exposure and risk assessment are performed. Subsequently, it is described, how a PPERI can be calculated. For proof of principle, four currently authorized plant protection products were used to calculate the re-entry time. These products were selected since the EFSA OPEX calculation resulted in a safe re-entry with gloves only (taking into account the data which is publicly available).

Dermal absorption

Information on the current scientific position on dermal absorption for the formulation, spray dilution and dried residue and its relevance for the approval of PPP's worker scenario was retrieved via a literature search and reported.

Toxic properties of dried substances

The question about differences in toxicological properties of the active substances (a.s.) between dried residues and dilutions of PPPs is discussed, in view of acute toxicity, skin irritation and sensitization, by presenting the CLP calculation rules for mixtures. In addition, a literature search was performed to explore studies focusing at properties of the spray dilution and the dry foliar residues of products.

2 Calculation of Personal Protective Equipment Required Interval -

2.1 Pesticide exposure for workers and the Personal Protective Equipment Required Interval

Re-entry intervals (REI) for workers are defined as “[...] the minimum amount of time that must pass between the time a pesticide was applied to an area or crop and the time that people can go into that area without protective clothing and equipment”, according to the Canadian Centre for Occupational Health and Safety (CCOHS) (www.ccohs.ca). There is no EU harmonised definition for re-entry interval.

In general, exposure to pesticides and pesticide residues may occur by inhalation of vapours, dusts or mists, skin contact with residues, eye contact with vapours, dusts or mists, or by rubbing eyes with a hand, a glove or clothing that is contaminated with pesticide residue and ingestion (eating food that has been treated or eating without first washing hands). Inhalation exposure may potentially occur from residual vapour and airborne aerosols through handling of the crop during re-entry activities (inspection, irrigation, harvesting). However, for outdoor situations (field) there will be more rapid dissipation of vapour and aerosols, leading to lower inhalation potential than from indoor treatments (greenhouses) (Guidance for post-application (re-entry worker) exposure, HSE UK). In general the main route of exposure to pesticide residues for workers is dermal, due to contact with the treated plant and manual crop handling, therefore the current report mainly focusses on the dermal exposure pathway for workers. During the re-entry time (REI), processes such as degradation and volatilization may lead to the reduction of the initial pesticide deposit on the crop while dry (dust) or wet (rain) deposition may contribute to the deposit on the crop.

The extent of the exposure is mainly influenced by the intensity of the contact with the crop, the amount of dislodgeable residue on the crop and the duration of the contact. During crop handling tasks, the skin of the worker can either be bare or covered by clothing and/or Personal Protective equipment (PPE). Clothing and PPE provide the worker a certain level of protection, because only a fraction of the transferred PPP migrates through the clothing and PPE and reaches the skin.

It is important to point out the difference between potential dermal exposure, actual dermal exposure and dermal absorbed dose. Potential exposure is the total amount of pesticide coming into contact with the protective clothing, work clothing and exposed skin. Actual exposure is the amount of pesticide coming into contact with exposed skin and the fraction migrating through protective and work clothing (OECD, 1997). The absorbed dose is similar to the systemic exposure, which defines the amount of a substance that migrated from the outer surface of the skin into the circulatory system (EFSA, 2012a).

As aforementioned, REI is set to protect workers against exposure to pesticides. In Europe however a PPP must be safe to enter directly after which a crop is dry (2 hours after application) to grant an authorisation for use. PPE (gloves) can be used to refine the risk in the risk assessment for authorisation. There is currently no PPE required interval determined (PPERI). In the Netherland the STIGAS recommends a default-PPERI of 14 day for safe re-entry (found at STIGAS/Fytostat.nl). After the PPERI elapsed, workers can perform crop task without wearing gloves but typical work clothing. And workers' exposure to pesticide residues is considered as safe when exposure does not lead to exceedance of the health based guidance value for the particular substance.

Currently there is no harmonized methodology proposed in the EU to determine the period for which gloves should be used when re-entering after application of PPPs. Present, the authorization assessment of PPPs does not involve the determination of a crop and product specific the time period to use gloves during re-entry tasks (PPERI).

2.2 Workers' exposure assessment update in EU and NL: EFSA OPEX model

The European Food Safety Authority, EFSA released 2014 the 'Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products' (EFSA 2014) and a new exposure model the EFSA OPEX model (simple excel spreadsheet), both published at the EFSA webpage (<https://efsa.onlinelibrary.wiley.com/doi/abs/10.2903/j.efsa.2014.3874>). The risk of exposure to pesticides can be calculated simultaneously for different people categories: operator (applies pesticide at crops), worker (crop maintenance and harvest), residents and bystander. EFSA explains in detail the algorithms and default values in the guidance document on assessment (EFSA 2014) and in the 'Guidance on dermal exposure' (EFSA, Buist et al. 2017), to be used for exposure assessment.

Until December 2015, 'worker re-entry exposure' assessments for in the EU authorized plant protection products (PPP) were performed in the Netherlands (NL) according to Dutch authorization Handbook (Handboek toelating en beoordeling) (HTB 1.0), using EUROPOEM II model, offering the 2 scenarios: field and greenhouse applications (EUROPOEMII 2002). For indoor operator exposure assessment (manual spraying) the Dutch greenhouse model (Dutch-exposure-model 1992) was used.

Since January 1st 2016, the NL follows the EFSA guidance document and uses the EFSA OPEX model for exposure assessment for all new PPP in field ('outdoor') and greenhouse ('indoor') applications. This RIVM report considers only field application for the exemplary calculation of exposure and re-entry times for 4 PPP, as a proof of principle. The main calculation steps are briefly reported hereafter, including dislodgeable foliar residue, transfer coefficient, task, dermal absorption and inhalation.

2.3 EFSA-OPEX model: mathematical algorithm

2.3.1 Total potential systemic exposure

(See Annex Figure A1 screenshot of data entry page of excel spreadsheet of EFSA OPEX)

The EFSA OPEX model calculates the total potential systemic exposure (TSE). Under the assumption that the main route of exposure for workers in crops of field application is dermal, and inhalation is neglected the TSE to pesticide residues on foliage, is estimated as product of dislodgeable foliar residue (DFR), (dermal) transfer coefficient ($TC_{(derm)}$) task duration (WorkHr) and multiple application factor (MAF), divided by dermal absorption factor for the in-use dilution (DA_{dil}) of the PPP according to eq. 1.

$$TSE = \frac{DFR \times TC_{derm} \times WorkHr \times MAF}{1000 \times DA_{dil}} \text{ (eq. 1)}$$

<i>TSE</i>	Total potential exposure (TSE) (mg a.s. /day) =
TC_{derm}	Transfer Coefficient (cm^2/h) = Dermal Transfer Coefficient (TC_{derm})
<i>DFR</i>	Dislodgeable Foliar Residue (μg a.s./ cm^2 / 1000)
<i>WorkHr</i>	Working hours (h/day)
<i>MAF</i>	Multiple application factor
DA_{dil}	Dermal absorption factor (of PPP in-use dilution)

2.3.2 Toxicological reference value

The workers' exposure (result of the EFSA OPEX model) was compared to a toxicological reference value (Reference Value for Non-acute Active Substances, RVNAS). For the exposure assessment during the authorization of PPP, the acceptable operator exposure level (AOEL) is the toxicological reference value for non-dietary exposure to pesticides (thus AOEL = RVNAS).

The RVNAS is defined as a level of daily exposure throughout a spraying season, below which no adverse systemic health effects would be expected.

The potential total exposure (TSE) is calculated with the EFSA OPEX model and compared to the RVNAS. In the EFSA OPEX model the TSE is the sum of the potential inhalation exposure (PIE) and the systemic dermal exposure (SEWd). The PIE is negligible in the occupational setting for workers for field application after the drying period for the sprayed crops. Moreover, gloves are not a protective measure against inhalation exposure. Therefore the RIVM refers to systemic exposure as SEWd for field applications. The main exposure route for workers during field applications is dermal.

2.3.3 Dermal exposure calculation (SEWd)

The systemic exposure of worker via the dermal route (SEWd) is required as an input parameter for the calculation of the Personal Protective Equipment Required Interval (PPERI) for workers entering pesticide sprayed crops. The SEWd is calculated with eq.2.

$$SEW_d = \frac{DFR \times TC_{derm} \times WorkHr \times MAF}{1000 \times DA_{dil} \times BW} \quad (\text{eq.2})$$

SEW_d Systemic exposure of worker via the dermal route (mg/kg bw/day)

BW Body weight (adult default is 60 kg)

To calculate the systemic dermal workers exposure a correction is made for body weight (adult default is 60 kg), i.e. the dermal systemic dose expressed as [mg a.s./kg bw /day].

2.3.4 Input parameters

DFR and MAF

The dislodgeable foliar residue (DFR) is the product of a default value for dislodgeable foliar residue at t=0 (DFR₀ = 3 µg a.s./cm² of foliage per kg a.s. applied per ha) and a reduction of a.s. through dissipation.

Applicants can use experimentally determined DFR data from studies that are specifically designed for this purpose. The DFR depends on several factors, including application rate, application efficiency (how much reaches and is retained on the target), crop type and the amount of foliage (leaf area index).

$$DFR = DFR_0 \times AR \quad (\text{eq. 3})$$

DFR	Dislodgeable Foliar Residue (µg a.s./cm ²)
DFR ₀	Default Dislodgeable Foliar Residue at t= 0 (3 µg a.s./cm ²), no dissipation
AR	Application rate (kg a.s. per ha)

Additionally EFSA OPEX assumes that not all the residues from earlier spray events are completely dissipated before a new spray event in case of multiple spray application (i.e. in orchards). The amount of residue on crop foliage decreases by dissipation as time increases. Dissipation itself depends on the physical and chemical properties of the applied PPP, but also on environmental conditions. As default EFSA OPEX assumes the worst case scenario, the dissipation (DT50) of a substance with a half-life of 30 days. However, when available from specific studies the default may be replaced by the DT50 as determined in that study.

The influence of repeating spray event in a certain time-window (once a week or every two weeks, etc.), e.g. the amount of residues still present at time of the new spray event is taken into account together with the new present residue due to the new spray event. In case of multiple spray events, the model corrects the foliar residue concentration with the multiple application factor (MAF). In the calculation of the MAF, the build-up of residues is expressed by the number of applications (n). A MAF_m factor, for use with average mean residue unit doses data, is calculated using the following equation:

$$MAF_m = \frac{1 - e^{-nki}}{1 - e^{-ki}} \quad (\text{eq.4})$$

where:

MAF_m Multiple application factor average mean residue unit doses data
k ln(2)/DT50 (rate constant)

n *Number of applications*
 I *Application interval (days)*

Assuming the limit value, $\lim_{n \rightarrow \infty}$, of the equation above, the term e^{-nki} becomes zero and a "plateau" MAF_m for an infinite number of applications can be calculated.

In simple words, EFSA OPEX calculates the maximum amount of residues after multiple applications taking DT50 into account.

TC

The TC reflects the transfer of residues from the plant surface to the cloth or skin of the worker. Regardless of the product applied, the level of transfer depends on the intensity and duration of contact with the foliage, e.g. residue transfer while picking strawberries is smaller due to activity and contact area compared to harvesting and bundling of ornamentals.

The model (EFSA 2014) offers the selection of grouped tasks for crop re-entry activities: clustered by crop habitats (leaf area and density) and re-entry activities as shown in Annex Table A1.

For the seven groups of re-entry tasks the model presents 16 different (dermal) transfer coefficients (TC) values to describe the transfer of residues from foliage. EFSA OPEX presents 19 unique combinations of crops and task in a picklist. By default EFSA OPEX assumes TC values for workers dressed in shorts wearing T-shirts with no sleeves and no gloves for the potential dermal exposure calculation. Thus a worst-case scenario with high surface area of bare skin is considered. The dimension of the foliar residue transferred (TC) is reduced when selecting work clothing as default, covering body, legs and arms (n=19). A bigger reduction foliar residue transfer of the TC (n=13) is achieved when selecting the default work clothing (body, arms and legs covered) including protective gloves. Thus, the selection of the second and latter default TC's reflects a higher level of protection as a result of using these two levels of PPE. The model does not give additional refinement options, such as protective coveralls and/or gloves with high protection. The model offers eight different (grouped) crops (e.g. small fruits pome fruits, ornamentals, trees, cereals, ect.) available for spraying. Selection of a crop group results in an automatic selection of crop specific task TC.

2.3.5 *Dermal absorption (DA)*

EFSA advises in the 'Guidance on Dermal Absorption' (EFSA, Buist et al. 2017), to use the following default values for organic solvent-based products, DA 25 % and 70 %; and for water-based and solid products, DA 10 % and 50 %, for the undiluted product and the in-use dilution, respectively, in order to assess of worker, resident and bystander exposure towards surface deposits. Higher DA default values (70 % for organic solvent-based formulations and 50 % for water-based and solid products) are selected to calculate the dermal exposure as a conservative approach (ESFA guidance, 2017). Present, for the majority of PPPs experimentally determined DA values for dried residues after application of spray dilutions are not available due to the lack of a harmonized experimental methodology. However, applicants may refine the DA default values, by entering study specific DA values for the

product and in-use spray dilution, if determined from dermal absorption experiments.

2.3.6 *Task duration or work hours (WorkHr)*

The default value for task duration is eight hours for harvesting and maintenance type activities and two hours for crop inspection and irrigation-type activities.

2.3.7 *The inhalation re-entry exposure*

Inhalation (PIE) is likely to contribute only to a minor extent to the total potential exposure during re-entry of workers in crop fields and is therefore negligible in the occupational setting (field). The main exposure route for workers during field applications is dermal (SEWd). Only for indoor scenarios, such as re-entry in greenhouses, the inhalation exposure needs to be calculated. Task-specific inhalation factors are used for first tier exposure assessments (e.g. relating to harvesting tasks indoors and to re-entering greenhouses where pesticide droplets may remain airborne after the treatment). Inhalation exposure for this re-entry scenario is estimated according to the following equation:

$$PIE = AR \times TF \quad (\text{eq. 5})$$

PIE Potential inhalation exposure [mg a.s./h inhaled]

AR Application rate [kg a.s./ha]

TF Task Specific Factor [$\text{ha/h} \times 10^{-3}$]

The Task Specific Factors are cutting (0.1), and for ornamentals sorting and bundling (0.01), Re-entering greenhouses after low-volume-mist application (0.03; 8 h after application) and re-entering greenhouses after roof fogger application (0.15; 16 h after application). (van Hemmen, Chester et al. 2002, Table 14 from EFSA, 2014)

Inhalation exposure is calculated for low ($< 5 \times 10^{-3}$ Pa) and moderately volatile (5×10^{-3} Pa and 10^{-2} Pa) active substances only for greenhouse (indoor) applications. However, levels of inhalation exposure (vapour and dust) are expected to be low in comparison with dermal exposure in indoor and outdoor re-entry worker scenarios. Additional data may be necessary for products applied as vapours and for volatile pesticides to calculate inhalation exposure, but according to EFSA (2014) such pesticides are outside the scope of the Guidance.

2.4 **Personal Protective Equipment required interval (PPERI) for crop workers**

2.4.1 *Rationale for calculation of Personal Protective Equipment required interval (PPERI)*

For the outdoor (field) post-application exposure of (unprotected) workers in crop harvesting fields where multi-spraying events have been applied, EFSA OPEX calculates the dermal systemic exposure for workers (SEWd in mg a.s./kg bw/day).

In case the SEW_d is smaller than the RVNAS for such exposure, work without exposure protecting measures is safe immediately after the final spraying event. If SEW_d exceeds the RVNAS, work without exposure protecting measures, an authorization cannot be granted without mitigation measures. Possible risk mitigation measures may be taken such as personal protective equipment (PPE) for safe re-entry into crops. The EFSA OPEX model can also calculate the dermal systemic exposure for workers with PPE (gloves).

The RIVM proposes an approach to calculate the PPERI, when elapsed, allowing the worker in work cloths to enter the crop without PPE.

Starting from the EFSA OPEX model for exposure assessment, equation 1 to calculate the potential total exposure (TSE) was used, which contains the parameters: dislodgeable foliar residue (DFR), the dermal transfer coefficient (TC_{derm}) and the task duration (WorkHrs) and the MAF were used to derive at the PPERI equation

2.4.2 Calculation of PPERI

EFSA OPEX: Calculation of the Total Systemic Exposure

As TSE is the same as SEW_d under the assumption that inhalation does not add to the TSE, the SEW_d is calculated for a multi-spraying event as follows in equation 6.

$$SEW_d = \frac{TC_{derm} \times WorkHr \times DFR \times MAF}{BW \times 1000} \times DA_{dil} \quad (\text{eq.6})$$

SEW _d	Systemic Dermal Exposure Worker (mg a.s./kg bw/day)
TC _{derm}	Dermal Transfer Coefficient-Total potential exposure (cm ² /h)
WorkHr	Working hours (h/day)
DFR	Dislodgeable Folar Residue (µg a.s./cm ²)
MAF	Multiple Application Factor (dimensionless)
1000	µg → g conversion factor
BW	Body Weight (kg)
DA _{dil}	Dermal Absorption factor of the in-use solution

The appropriate PPERI may be obtained by taking the decay of the a.s. as occurring under field conditions after the final spraying event into account (one-compartmental, first order decay). For a PPERI of zero, the decay of the a.s. should have progressed, resulting in a decreased SEW_d such that it has reached the level of the RVNAS.

This results in the following equation:

$$RVNAS = SEW_D \times e^{-\frac{\ln 2}{DT_{50}} \times REI} \quad (\text{eq.7})$$

This can be solved, for PPERI:

$$PPERI = \frac{-\ln\left(\frac{RVNAS}{SEW_D}\right) \times DT_{50}}{\ln 2} \quad (\text{eq. 8})$$

RIVM proposes the above outlined approach as basis for a harmonised methodology to estimate the pesticide-specific and agricultural-use related PPERI for PPPs.

3 Dermal absorption of dried residues and testing & the properties of the spray dilution and dried residue

3.1 Literature search

To answer the questions: *What is the current view on dermal absorption of dry substances (with regard to worker exposure during re-entry and relevance for approval of PPP's worker scenario)? Do spray dilutions of products with properties like acute toxicity, skin irritation and or sensibilization, keep their properties and for which period? Do these product properties apply (and for which period) also for their foliar residues?*, information was retrieved from the scientific literature.

The literature searches were performed with the search criteria: acute toxicity incl. skin irritation of PPP and of dried residues of PPPs, dermal absorption of concentrate and/or dilution of PPP and/ or dried PPP residue)

The databases used were Medline, Embase (via Embase. com) and Scopus to find studies for i) acute toxicity of pesticide dilutions, ii) acute toxicity of dried residues and iii) dermal absorption for the publishing period of 2005 till November 2017. The specific search terms are given in the annex figure A2, A3 and A4, for i), ii) and iii), respectively.

The search resulted in a total revenue of, 143 items (96 Embase. com + 47 additional items from Scopus), 37 items (24 Embase. com + 13 additional items of Scopus) and 32 items (15 Embase. com + 17 additional by Scopus), respectively.

Resulting publication were screened with regard to question 2), 3) a. and b. and 4) and new findings were reported in Chapter 3.

3.1.1 *Dermal absorption*

The dermal route is the primary route of exposure for most pesticides in occupationally settings.

The PPP dossier for authorization in most cases contains a 28-day dermal general toxicity study which does not cover some endpoints (e.g. developmental or reproduction toxicity). For practical reasons toxicity studies for registration purposes are dosed via the oral route. To perform a proper risk assessment for dermal exposure, dermal absorption data is required to calculate the dosage in the body.

Dermal absorption, the process by which a substance is transported across the skin and taken up into the body, is a complex process often divided in penetration, permeation and resorption. The skin is a multi-layered biomembrane (Figure 1, (OpenStaxCollege)) with particular absorption characteristics. It is a dynamic, living tissue and as such its absorption parameters are continuously susceptible to changes. Upon contact with the skin, a portion of the substance can permeate through the *stratum corneum* and may subsequently reach the epidermis, the dermis and ultimately, the vascular network (Figure 2 (OpenStaxCollege)).

Permeation is basically a diffusion process in which active transport plays no role. The *stratum corneum* provides the skin its greatest barrier function against hydrophilic compounds, whereas the epidermis is most resistant to highly lipophilic compounds. During the absorption process, the compound may be subject to biotransformation. (EHC_235 2006) After the chemical diffuses in the mainly aqueous environment (living epidermis and dermis), it is taken up into the cutaneous blood and lymphatic system (resorption). However, compounds can accumulate in the viable epidermis, in the dermis, and in deeper tissues if blood flow is insufficient.

Dermal absorption can be influenced by several factors, e.g. physico-chemical properties of the substance, vehicle (solvent in which the active substance is dissolved), occlusion of the treatment site, concentration, exposure pattern and skin site of the body. In order to harmonize the use of dermal absorption data in human risk assessment, OECD developed testing protocols for in vitro and in vivo dermal absorption studies (OECD 2004, OECD_TestNo.428 2004). Additionally an EFSA guidance document was prepared in 2012 and revised in 2017 (EFSA, Buist et al. 2017) for harmonized study evaluation.

3.1.2 *Dermal absorption test studies*

In vivo skin absorption studies for risk assessment purposes are most often performed on laboratory rats. An advantage of the rat is that this is the species used in most toxicological and kinetic studies. On the other hand, it is known that data from rat studies generally overestimate human skin absorption. The preferred dermal absorption study is the in vitro dermal absorption study. In vitro experiments are an appropriate surrogate for in vivo studies and offer a number of advantages over whole-animal experiments. In vitro methods measure the diffusion of chemicals into and across skin to a fluid reservoir and can utilize non-viable skin to measure diffusion only or fresh, metabolically active skin to simultaneously measure diffusion and skin metabolism. Additional advantages are that in vitro methods are saving time and costs, have better reproducibility of results, and have less restricted parameter variations (van Ravenzwaay and Leibold 2004). In vitro skin absorption studies can be performed in a variety of diffusion cell types. All cells consist of a donor and receptor compartment but may differ with respect to surface area, type of material and volume. Despite the differences between cell types, it appears that the data obtained are very similar (Clowes, Scott et al. 1994).

Human skin membranes used in the in vitro tests are usually prepared from abdominal or breast skin, while for animal skin membranes the commonly used sites are the flank and back. Three types of membranes can be prepared: epidermal membranes (thickness of approximately 0.1 mm, prepared by heat separation, chemical or enzymatic separation, split-thickness skin (thickness of 0.2-0.5 mm prepared by using a dermatome) and full-thickness skin (thickness of 0.5-1.0 mm). Since the main barrier function of the skin is located in the *stratum corneum*, all three membrane types have been used for absorption studies.

A possible disadvantage of full-thickness skin is that lipophilic compounds may be retained in the dermis instead of entering into the

receptor fluid. In contrast, epidermal membranes are more fragile and may overestimate human in vivo skin absorption. (van de Sandt, Meuling et al. 2000). More important, in vitro studies cannot be used for prolonged dermal absorption studies (max. 24 hrs) to mimic stay-on products or to mimic repeated exposures because the skin membranes will disintegrate(OECD_TestNo.428 2004).

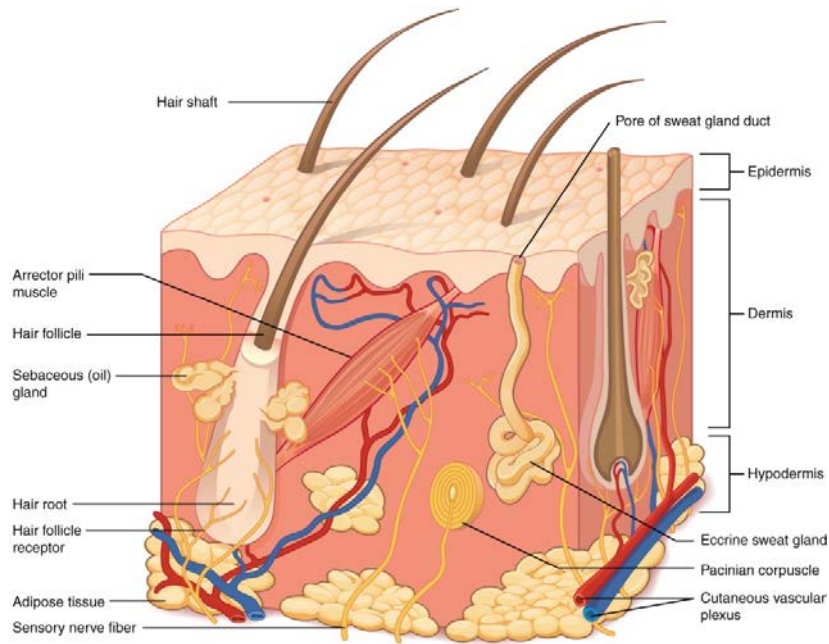


Figure 1: Skin section with the 3 layers epidermis - most superficial, dermis and hypodermis/subcutaneous tissue

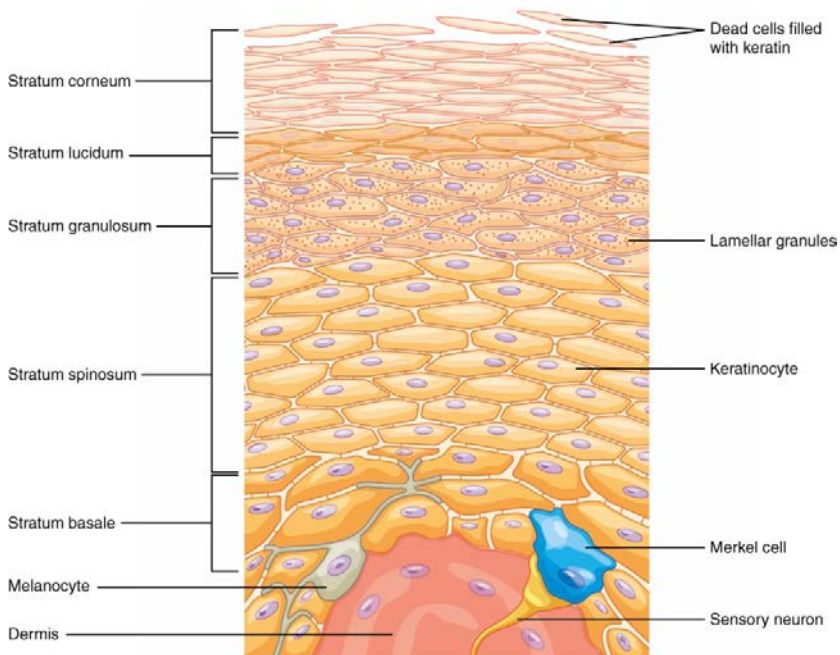


Figure 2: Five layers of the epidermis: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum

4 Results

4.1 Worker's exposure (SEWd) during re-entry

Note: The RIVM wants to point out that all presented results and calculations for the SEWd do not aim at performing a re-assessment of PPP-exposure but serve as case study examples to develop methodology.

The dermal systemic exposure for workers (SEWd) was calculated with the EFSA OPEX model for 4 PPPs (Tab. 3-1).

Default values and specific study data (e.g. DT50, DA, AR) from the applicant's dossier which are publicly available at the Ctgb website (CTGB 12-2017) were used as input data for the model, and are given in Tab 3-1. SEWd for workers re-entering crop fields (orchards, small fruits and ornamentals) for crop related tasks (reach and pick) that were sprayed, was calculated. The results for the 2 exposure scenarios a) long sleeve work clothing (body, legs and arms covered, bare hands) and b) long sleeve work clothing and protective gloves are presented in Tab. 3-1, both scenario's are used for PPP authorisation.

The exposure SEWd was compared to the RVNAS and is presented as percentage of the RVNAS. Values below 100 % mean that no potential health risk can be expected because the RVNAS was not exceeded. Exceedance of the RVNAS means the exposure may lead to a potential health risk for workers is indicated by values above 100 %. If exposure exceeds the RVNAS, the PPERI can be calculated. During the period of PPERI re-entry into treated crops without PPE should be avoided. If crop related tasks are required before the PPERI elapses, workers are should wear gloves as additional protective measures for a safe re-entry into the crop field.

The SEWd calculation for the active substance bupirimate (Nimrod Vloeibaar), mepanipyrim (FireBlocker), tebuconazole (Folicur) pendimethalin (Stomp) were performed and served as case studies. SEWd values without gloves are higher than 100% of the RVNAS, testing scenario a). The use of gloves is therefore required for workers to safely re-enter the treated crops. Therefor a PPERI was estimated for these PPPs, to demonstrate the proof of principle of the methodology for PPERI calculation (See 4.2, Tab. 3-2).

Considering mitigation scenario b) (work clothing and gloves) the calculated SEWd for the active substance bupirimate (Nimrod Vloeibaar), mepanipyrim (FireBlocker), tebuconazole (Folicur) and pendimethalin (Stomp) resulted in % of RVNAS values below 100%, and therefor exposure to PPP residues did not exceed the RVNAS. SEWd values below the RVNAS leads to the conclusion that no adverse health effects for workers, are expected (Tab 3-1).

The model calculated the exposure using different TCs for the crop types for the scenario a), for pome fruits (4500 cm²/h), small fruits (3000

cm²/h), and ornamentals (5000 cm²/h). These TCs are reduced by a factor of 2, 4 and 3.6 when selecting the risk mitigation option b) of wearing work clothing and protective gloves (Table 13, EFSA 2014).

Table 3-1: Dermal systemic exposure (SEWd) assessment for workers, testing 2 scenarios: a) wearing work clothing and b) work clothing and gloves, when directly re-entering crops after typical spray application of 4 PPP for 3 different crop categories (orchards, small fruits, ornamentals)

Crop category/ application	Product name (formula)	Active substance (a.s.)	SEWd (mg/kg bw/day)		% of RVNAS ^{\$}		AR* a.s. (kg /ha)	RVNAS (mg/ kg bw/ day)	N	INT (day)	DT50 (day)	Dermal absorption factor [#]	
			Work Cloth a)	Work cloth and gloves b)	Work cloth	Work cloth and gloves						Product	In-use
Small fruits (strawberry)	Nimrod Vloeibaar (EC)	bupirimate	0.11	0.026	211	53	0.25	0.05	4	10	30	0.013	0.12
Ornamental plants (tulips)	FireBlocker (SC)	mepanipyrim	0.16	0.044	225	63	0.154	0.07	10	7	30	0.0026	0.952
	Folicur (WG)	tebuconazole	0.036	0.01	120	33	0.138	0.03	1	365	30	0.05	0.13
	Stomp (SC)	pendimethalin	0.53	0.15	311	87	0.8	0.17	1	365	30	0.004	0.33

N – Number of spray applications

INT – Interval between spray events

* Application Rate

\$ NOTE: if % of RVNAS equals 100 or less, the exposure did not exceed the RVNAS

Default values (EFSA 'Guidance on dermal absorption' (EFSA, Buist et al. 2017) for dermal absorption depending on the formulation type emulsifiable concentrate (EC), suspension concentrate (SC), water-dispersible granules (WG/WDG),

-Specific study values (Interval and number of applications) were taken from publicly available dossiers are highlighted with grey background DT50 of 30 days are default values.

Note:

The EFSA OPEX model calculates the TSE for the workers (TSE = SEWd, which is compared to the RVNAS and should be smaller than the value of the RVNAS for safe exposure levels for workers.

4.2 Safe re-entry time (PPERI) for workers

Note: The RIVM wants to emphasize that all presented results and calculations for the PPERI do not aim at performing an additional assessment of exposure safety for previously authorized PPP (exposure assessments were performed applying other legitimate models before 2016) in the Netherlands.

The RIVM calculated the PPERI (eq. 8) for the 4 PPPs, where the SEWd exceeded the RVNAS: Nimrod Vloeibaar, FireBlocker, Folicur and Stomp, containing the active substance bupirimate, mepanipyrim, tebuconazole and pendimethalin, respectively. The PPERI was calculated based on their dermal systemic exposure results (SEWd mg a.s/kg bw/day), which revealed the exceedance of the RVNAS, indicated by a % of RVNAS greater than 100% as presented in section 4.1, Tab. 3-1.

If crop-related task are required before the PPERI elapses, workers are advised to wear additionally protective gloves. For how long gloves need to be worn as mitigation option depends on the day of re-entry after the date of PPP application (after last spray event) for the period of PPERI, for 32, 35, 8 and 49 days (related to day 0 of spray application), if the PPP Nimrod Vloeibaar, FireBlocker, Folicur and Stomp were applied according to the agricultural practice indicated at the label (Tab. 3.1), respectively.

Table 3 -2: Safe re-entry time (PPERI) after typical spray application of 4 PPPs for 3 different crop categories (orchards, small fruits) for one worker's exposure scenario: a) wearing working cloth but no gloves, are presented; re-entry without gloves after respective PPERI will result in worker's exposure not exceeding the RVNAS (health based guidance value)

Crop category/ application	PPP name (formulation type)	Active substance (a.s.)	PPERI (days) Work Cloth a)*	% of RVNAS [§]		AR* a.s. (kg /ha)	RVNAS (mg/kg bw/day)	Number of appli- cations	Interval (day)	DT50 (day)	Dermal absorption factor [#]	
				Work cloth	Work cloth and gloves						Product	In-use dilution
Small fruits (strawberry)	Nimrod Vloeibaar (EC)	bupirimate	32	211	53	0.25	0.05	4	10	30	0.013	0.12
Ornamental plants (tulips)	FireBlocker (SC)	mepanipyrim	35	225	63	0.154	0.07	10	7	30	0.0026	0.952
	Folicur (WG)	tebuconazole	8	120	33	0.138	0.03	1	365	30	0.05	0.13
	Stomp SC	pendimethalin	49	311	87	0.8	0.17	1	365	30	0.004	0.33

* Workers wear work clothing where body, arms and legs are covered

Specific study values taken from publicly available dossiers are highlighted with grey background

4.3 Dermal absorption of dry foliar residues of PPP

This chapter deals with the question 'What is the current view on dermal absorption of dry substances, i.e. residue exposure during re-entry and how is it relevant for approval of PPPs?'. Currently there is a lack of experimental studies, unified study designs and a common agreement on a harmonized approach, how to evaluate dermal absorption of dried residues, which may become relevant for the authorization of PPPs in the future, with regard to dermal exposure for workers exposed to sprayed crops.

4.3.1 *Current view on worker-related dermal absorption testing*

Workers when allowed to re-enter an area previously treated with a pesticide are exposed to dried residues of the diluted product. However for pesticide regulatory purposes studies are performed with the concentrate formulation (liquid) or moistened concentrate formulations (powder or granule) and aqueous in-use (spray) dilutions. Currently there is no reliable *in vitro* test or acceptable methodology to estimate dermal absorption of pesticides from the dried and diluted residue. In *in vitro* testing the skin membrane should be moistened to maintain skin integrity and avoid damage.

Arguments can be made to support the use of either the concentrate or the dilution value to estimate the dermal absorption of a dried, diluted residue ((HSE) guidance for post-application (re-entry worker) exposure assessment).²

The following arguments suggest the most appropriate dermal absorption value is that one for the dilution;

- The dried residue from the diluted product will give rise to a low mean mass per unit area. This is more closely related to the testing of the in-use-dilution than to the concentrate.
- Dermal absorption can show saturation if the mass per unit area exceeds a certain level. The dried residue has a low mass per unit area and hence the level of saturation would be expected to be in line with that for the dilution.

The following arguments suggest the most appropriate dermal absorption value is that for the concentrate.

- The dermal contact is with a dried residue. This absence of water has been shown to reduce dermal absorption in some studies. This situation can therefore be considered more closely related to exposure to a liquid or solid concentrate than a highly diluted product.
- If the concentrate / solid is irritating this can increase blood flow to the skin resulting in enhanced dermal absorption. The dried residue can potentially have localized high concentrations (e.g. particles from a suspension) that might be irritating resulting in enhanced absorption.

² This document does not replace the approach outlined in the European Food Safety Authority (EFSA) guidance document on the assessment of operator, worker and resident & bystander exposure to plant protection products, but may be used in the absence of relevant guidance.

Because of these uncertainties the conservative approach of using the higher of the values derived for the concentrate and dilution is applied for dried dispersed residue (EFSA, Buist et al. 2017)

4.3.2 EFSA's opinion: Dermal absorption

EFSA states in the updated guidance on dermal absorption (EFSA, Buist et al. 2017) that DA which is estimated in field monitoring studies of workers/operators is rarely accurate due to difficulties in measuring skin deposition and knowledge about the metabolism in humans. Therefore, EFSA considers that data obtained from field studies are only applicable to support experimentally determined values.

The updated guidance for dermal absorption of 2017 (EFSA, Buist et al. 2017) contains the statement about how to choose the best dermal absorption value for worker and resident exposure:

*"5.10. Choice of dermal absorption values for worker/resident exposure
Until the outcome of the ongoing research into this aspect is available and conclusions have been drawn, it is proposed that the appropriate dermal absorption value for exposures to dried dispersed residue should be the higher of the values for the concentrate and the in-use dilution. If an acceptable estimate of worker/resident exposure cannot be obtained using this approach, specific evaluations could be performed on a case-by-case basis. These could take into account factors such as the level of the dislodgeable foliar residue (mass/unit area) and transfer coefficient vs the loading used in the dermal absorption studies with concentrate and dilution(s) to help determine the most appropriate dermal absorption value to use. Any lowering of default values commonly applied in exposure models should be justified."*

EFSA gives the following default values (accord. EFSA 'Guidance on dermal absorption' (EFSA, Buist et al. 2017) for dermal absorption depending on the formulation type (Tab. 4). A default dermal absorption value of 25 % for the concentrate and 70 % for the in-use dilution may be applied for organic solvent-formulated (a) or in other (b) types of formulations. A default dermal absorption value of 10 % for the concentrate and 50 % for the in-use dilution may be applied for water-based/dispersed(c) or solid formulations.

Table 4-1: Default values to be used in the absence of experimental data

Formulation type	Concentration status	Default value
Organic solvent-based ^{a)} or other ^{b)}	Concentrate	25 %
	Dilution	70 %
Water-based ^{c)} /dispersed or solid ^{d)}	Concentrate	10 %
	Dilution	50 %

a) organic solvent-based: emulsifiable concentrate (EC), emulsion, oil in water (EW), suspo-emulsion (SE), dispersible concentrate (DC), oil miscible liquids (OL/OF), oil-based suspension concentrates (OD), emulsion for seed treatment (ES), microemulsion (ME);

b) others: bait concentrate (CB), capsule suspension (CS), gel for direct application (GEL/GD), bait, ready for use (RB), mixture of capsule suspension and suspension concentrate (ZC), seed coated with a pesticide (PS), experimental solution of active substances in solvent (AI)

c) water-based/dispersed: soluble concentrate (SL), suspension concentrate (SC), flowable concentrate for seed treatment (FS), flowable (FL) (=SC);

d) solid: wettable powder (WP), water-dispersible granules (WG/WDG), water-soluble granules (SG), water-soluble powder (SP), powder for dry seed treatment (DS)

4.3.3 *New Literature*

The literature search (“dermal absorption”, “dried residues of pesticides”) in the online database resulted in 32 studies for dermal absorption. Screening the content related to the question, how dermal absorption differs between dilutions or dried substances, and in which way this fact may impact future PPP approvals, reduced the small number of suitable studies further, which are briefly summarized hereafter.

Previous work (Belsey, Cordery et al. 2011) has shown that pesticide absorption from a residue, when applied in the form of a coated disk pressed against the skin, was different from that of an aqueous solution and that the risk estimation for re-entry scenarios may be incorrect when using an aqueous solution or concentrate based methodology. However this long-term exposure was not fully representative of a re-entry worker scenario, where only brief contact between skin and foliage would occur. Moreover the doses applied were an order of magnitude higher than occurring in a real exposure scenario.

Recently, an assessment of an extended dataset of in vitro human dermal absorption studies on pesticides was carried out using a combination of the EFSA conservative option for dermal absorption (i.e., skin residue except first 2 tape strips is absorbed) and 95th percentile values of the datasets, to determine default values, opportunities for read-across and influence of dilution on absorption (Aggarwal, Fisher et al. 2015). The assessment supported defaults of 6% for liquid and 2% for solid concentrates irrespective of the active substance loaded. For all spray dilutions, irrespective of the formulation type a single default of 30% was concluded. Despite using EFSA’s worst-case definition for absorption, authors suggest that the entire *stratum corneum* residue and ideally the entire epidermal residue in *in vitro* studies can be excluded, based on their data set assessment.

A dislodgeable foliar residue study was conducted in greenhouse pepper and tomato on the island of Crete, Greece, following the spray application of an SC insecticide (with active substance (a.s.) tebufenozide) and an EC fungicide (a.s. bupirimate). Furthermore, for the assessment of worker exposure to pesticides – as a result of re-entering the treated crops – a worker dermal exposure study was carried out during the tasks of tying or pruning, which allowed the transfer coefficient values for the specific tasks to be determined. The results from the study resulted in transfer coefficient values which were in agreement with current EFSA guideline values in most of the cases with the exception of bupirimate in a tomato greenhouse. In that case, high potential dermal exposure and low dislodgeable foliar residue values were observed, which is thought to be due to the moist leaves collected during sampling and monitoring, which led to greater than expected transfer coefficient values. (Kasiotis, Tsakirakis et al. 2017)

4.3.4 *New in vitro dermal absorption testing methodology*

All pesticides must undergo a thorough risk assessment process in order to demonstrate their safe use. With respect to dermal risk assessment for re-entry workers, the absorption value applied to predict systemic dose from this external exposure is obtained by testing liquid forms of

the pesticide *in vivo* and/or *in vitro*. However, in real exposure scenarios, workers are exposed to a dried residue, for which little or no absorption data are available. Clark et al. (2015) developed a novel methodology for assessing dermal absorption of pesticides from dried residues (Clarke, Cordery et al. 2015) and aims ultimately to use this methodology to obtain more realistic absorption values for the risk assessment:

This methodology is based on a standard *in vitro* protocol to measure pesticide absorption (OECD 2004, OECD_TestNo.428 2004), using static Franz diffusion cells with dermatomed porcine skin and a receptor chamber containing the typical buffer solution. The pesticide was applied in 3 different physical states to the porcine skin, as emulsifiable concentrate (10% w/w) diluted 100-fold in water, or as a dried residue. For the residue a diluted concentrate was applied at steel discs, allowed to dry for 24 h and disc was then attached to a weighted vial (~10 g) that was rotated on the skin surface to achieve a transfer of a residue to the skin in to a workers comparable scenario. Post-application of the formulations, the receptor solution was sampled at 2, 4, 6, and 8 h. The skin surface was washed at 8 h (to represent a typical working day) with a mild soap. At 24 h an additional receptor sample was taken.

Results indicated that concentrations analytically determined in the receptor solution were slowly increasing over time (2-8 h) for the dried residue and catching up at time period between 8 - 24 h with the concentrations analyzed for the dilution, whereas highest residue concentrations in the receptor solution were determined at 24 h. A possible "washing-in" effect was neglected.

4.4 Toxic properties of spray dilutions and dry foliar residues of PPP

For the approval of an active substance and the authorization of a plant protection product, among others, acute toxicity, irritation and sensitization studies have to be provided (performed with the active substance and the plant protection product³) by the applicant. These studies are in most cases performed according to OECD testing guidelines, e.g. OECD TG 402 for acute dermal toxicity, OECD TG 404 for dermal irritation/corrosion and OECD TG 406 for skin sensitization. Most dossiers contain studies with the active substance and with the plant protection product. Plant protection products should be classified based on their toxic properties (EU Regulation (EC) No 1272/2008 (Regulation on Classification and Labelling, CLP)). This classification can result in obligatory risk mitigation measures (e.g. use of gloves by a P-phrase).

For acute toxicity, irritation/corrosion and sensitization high dosages/concentrations are tested. To obtain a spray dilution a plant protection product can be diluted up to 1000 times with water. No toxicity, irritation or sensibilisation studies are available for the dilution (or the dried foliar residue) where workers are exposed to. It is therefore unclear if the hazard classifications for acute dermal toxicity, irritation or sensibilization also apply for the spray dilution or dried foliar residue.

³ For plant protection products classification for acute toxicity, irritation and sensibilisation can also be based on the classification of the individual components in the product and the CLP calculation rules.

The question is therefore: Do the spray dilutions or foliar residues of plant protection products with acute toxic, irritation or sensibilization classification have similar toxic properties?

A literature search was performed to obtain information on the toxic properties of in-use dilutions and dried foliar residue, additionally classification rules for acute toxicity, irritation and sensibilization according to CLP is explained.

4.4.1 *Literature review of the toxic properties of in-use dilution and dried foliar residue*

The literature search in the online database (see 2.5) resulted in 143 and 37 studies for i) acute toxicity of pesticide dilutions and ii) acute toxicity of dried residues, respectively. Screening the content related to the specific question, if spray dilutions or foliar residues of PPPs with acute toxic, irritation or sensibilization classification have similar toxic properties, resulted in a small number of relevant studies reporting about the toxic properties of the substances, which are briefly summarized hereafter.

To a minor degree, dermal absorption may occur from exposure to great loads of PPP residues (Damalas and Koutroubas 2016). The severity of the toxic effect after dermal exposure depends on the dermal absorption, the toxicity of the pesticide, the duration of the exposure, the pesticide formulation, and the body part contaminated (Green et al, 1991). Powders, dusts, and granular pesticides are not absorbed so easily through the skin and other body tissues (e.g. mucous membranes) as are the liquid formulations. Liquid pesticides containing solvents (e.g., organic solvents) and oil based pesticides usually are absorbed more quickly than dry pesticides. For example, the emulsifiable concentrates, containing a great percentage of the toxic substance in a relatively small amount of solvent, are readily absorbed by the skin. Certain body areas are more prone to absorption of pesticides than other areas. (Damalas and Koutroubas 2016)

A questionnaire-based survey among workers from 3 flower farms (Africa) and control workers from supermarkets revealed high prevalence of respiratory and dermal symptoms, which are rarely reported among controls (Hanssen, Nigatu et al. 2015). Female workers operating in greenhouses at surveyed flower farms had significantly more respiratory and dermal symptoms than those working outside the greenhouse. Limited access to personal protection equipment (PPE) and unsafe pesticide routines are documented. The flower farm study indicated that working in these flower greenhouses might be associated with adverse health effects (Hanssen, Nigatu et al. 2015). However, worker conditions, hours and usage of PPE in underdeveloped African countries are less controlled (Negatu, Kromhout et al. 2016, Tadesse, Kelaye et al. 2016).

A survey was undertaken to establish the extent of pesticide exposure in a farming community, where acetylcholinesterase (AChE) was used as a marker for exposure assessment to organophosphorus insecticides. Changes in the AChE levels can lead to nervous system toxicity. Changes in this parameter can be used to evaluate long-term, or chronic, exposure. The outcomes of the study showed that exposure to

organophosphorus pesticides may cause DNA oxidative damage, inhibit AChE activity and increase the serum levels of inflammatory markers. The study lines out to advise the use of safety equipment by farmer workers to mitigate exposure to organo-phosphorous pesticides, resulting in the aforementioned adverse effects (Taghavian, Vaezi et al. 2016).

To summarize, powders and granular pesticides were mainly reported to not get absorbed so easily through the skin and other body tissues (e.g. mucous membranes) liquid formulations. As dried foliar residues have a solid physical state, and therefore may be less susceptible to absorption (Aggarwal, Fisher et al. 2015, EFSA, Buist et al. 2017). Recent studies on health effects due to exposure of workers to pesticide residues with toxic properties were mainly based on worker interview questionnaires and only occasionally on biomarkers, such as AChE for exposure assessment. There is a need of independent studies to capture health effects due to toxic properties of the sprayed product or dried residues, and their comparison.

4.4.2 *Toxic properties of spray dilutions based on CLP criteria*

The classification of substances and mixtures according to CLP criteria gives an indication of the toxic properties of the PPP and its ingredients. In June 2015, the Classification, Labelling and Packaging Regulation, No. 1272/2008, known as CLP, became fully operational in Europe for all chemicals, including plant protection products. All products placed on the market thereafter will need to comply, and the Regulation will be the key driver for harmonized classification and labelling of all PPPs. Plant protection products can be classified for acute toxicity, irritation and sensibilization based on actual toxicity studies with the marketed product or can be classified based on the classification of individual substances in the mixture. The relevant calculation methods used for the classification of mixtures are laid down in Regulation (EC) No 1272/2008 (Regulation(EC)No1272/2008 2008).

A spray dilution can be considered a mixture with (in most cases) a high content of water and with a lower concentration of substances as compared to the undiluted PPP. Guidance on the Application of the CLP Criteria (ECHA 2015) specifically addresses how to classify mixtures. No information is available how to estimate the toxic hazard and how to classify dried foliar residues (for which workers are exposed to) of mixtures. This is therefore not considered in this paragraph.

If the tested mixture is diluted with a substance (diluent) that has an equivalent or lower hazard category than the least hazardous original ingredient substance, then it can be assumed that the respective hazard of the new mixture is equivalent to that of the original tested mixture. This however can over-classify a mixture; therefore it is possible to use the additivity formula described in CLP Annex I, 3.1.3.6 by the *Regulation (EC) No 1272/2008* (Regulation(EC)No1272/2008 2008).

$$\frac{100}{ATE_{mix}} = \sum_n \frac{C_i}{ATE_i} \quad (\text{eq. 9})$$

Where:

C_i	Concentration of ingredient i (% w/w or % v/v)
i	Individual ingredient from 1 to n
n	Number of ingredients
ATE_i	Acute Toxicity Estimate of ingredient i
ATE_{mix}	Acute Toxicity Estimate of mixture

Consider using this particular bridging principle also when, for example,

- diluting an irritant mixture with water,
- diluting an irritant mixture with a non-classified ingredient, or
- diluting a corrosive mixture with a non-classified or irritant ingredient.

In most cases, test data on the mixture (or in this case the diluted mixture) itself will not be available. In these cases, classification must be based on calculation or on concentration thresholds referring to the classified substances present in the mixture. Therefore, it is necessary to know all ingredient substances, their hazard classifications and their concentrations to be able to derive a correct hazard classification of the final mixture.

For some hazard classes or differentiations, classification based on concentration thresholds may be applicable. CLP distinguishes between two different kinds of generic concentration thresholds:

- Generic cut-off values: these values are the minimum concentrations for a substance to be taken into account for classification purposes. When a classified substance is present in a concentration above the generic cut-off value it contributes to the mixture classification even if it does not trigger classification of the mixture directly. The generic cut-off values are defined for some hazard classes and categories only; and are listed in the table 3-5.

Table 3 - 1: Summary of generic cut-off values selected hazard classes and categories

Hazard Class	Generic cut-off values to be taken into account (for liquids)
Acute toxicity	
Category 1-3	0,1%
Category 4	1%
Skin Corrosion/Irritation	1%
Serious damage to eyes/eye irritation	1%

- Generic concentration limits: these values are the minimum concentrations for a substance which trigger the classification of a mixture if exceeded by the individual concentration or the sum of concentrations of relevant substances (where the individual substance concentrations can be 'added' to each other in a straight forward way).

Table 3 - 2: Generic concentration limits of sum of ingredients of a mixture for which the additivity approach does not apply that trigger classification of the mixture as corrosive/irritant to skin (taken from Table 3.2.3 of the CLP regulation)

Sum of ingredients classified as	Concentration triggering classification of a mixture as	
	Skin corrosive Cat1	Skin Irritant Cat 2
Skin Corrosive cat 1A, B and C	≥5%	≥1% but <5%
Skin irritant Cat 2.		≥10%
(10 × Skin Corrosive Category 1A, 1B, 1C) + Skin irritant Category 2		≥10%

Note: The sum of all ingredients of a mixture classified as Skin Corrosive Category 1A, 1B or 1C respectively, shall each be ≥ 5 % respectively in order to classify the mixture as either Skin Corrosive Category 1A, 1B or 1C. If the sum of the Skin Corrosive Category 1A ingredients is < 5 % but the sum of Category 1A+1B ingredients is ≥ 5 %, the mixture shall be classified as Skin Corrosive Category 1B. Similarly, if the sum of Skin Corrosive Category 1A+1B ingredients is < 5 % but the sum of Category 1A+1B+1C ingredients is ≥ 5 % the mixture shall be classified as Skin Corrosive Category 1C.

Table 3 - 3: Generic concentration limits of ingredients of a mixture for which the additivity approach does not apply that trigger classification of the mixture as corrosive/irritant to skin

Ingredient:	Concentration	Mixture classified as: Skin
Acid with pH ≤2	≥1%	Cat1
Base with ph ≥11,5	≥1%	Cat1
Other corrosive (Cat 1A,1B 1C) ingredients for which additivity does not apply	≥1%	Cat1
Other irritant (Cat 2) ingredients for which additivity does not apply, including acids and bases	≥3%	Cat2

Table 3 - 4: Generic concentration limits of ingredients of a mixture classified as Skin corrosive Category 1 and/or eye Category 1 or 2 for effects on the eye that trigger classification of the mixture for effects on the eye (Category 1 or 2)

Sum of ingredients classified as:	Concentration triggering classification of a mixture as:	
	Irreversible Eye Effects	Reversible Eye Effects
	Cat 1	Cat 2
Eye Effects Category 1 or Skin Corrosive Category 1A, 1B, 1C	$\geq 3 \%$	$\geq 1 \%$ but $< 3 \%$
Eye Effects Category 2 (10 × Eye Effects Category 1) + Eye effects Category 2		$\geq 10 \%$ $\geq 10 \%$
Skin Corrosive Category 1A, 1B, 1C + Eye effects Category 1	$\geq 3 \%$	$\geq 1 \%$ but $< 3 \%$
10 × (Skin Corrosive Category 1A, 1B, 1C + Eye Effects Category 1) + Eye Effects Category 2		$\geq 10 \%$

Table 3 - 5: Generic concentration limits of ingredients of a mixture for which the additivity approach does not apply that trigger classification of the mixture as hazardous to the eye

Ingredient	Concentration	Mixture classified as: Eye
Acid with pH ≤ 2	$\geq 1\%$	Cat1
Base with pH $\geq 11,5$	$\geq 1\%$	Cat1
Other corrosive (Category 1) ingredients for which additivity does not apply	$\geq 1\%$	Cat1
Other irritant (Category 2) ingredients for which additivity does not apply, including acids and bases	$\geq 3\%$	Cat2

Table 3 - 6: Generic concentration limits of ingredients of a mixture classified as either skin sensitizers or respiratory sensitizers that trigger classification of the mixture

Ingredient classified as:	Concentration triggering classification of a mixture as:		
	Skin Sensitizer All Physical states	Respiratory Sensitizer Solid/Liquid	Gas
Skin Sensitizer	≥ 0,1 % (Note 1) ≥ 0,1 % (Note 2)		
Respiratory Sensitizer		≥ 0,1 % (Note 1) ≥ 0,1 % (Note 3)	≥ 0,1 % (Note 1) ≥ 0,1 % (Note 3)

Note 1: This concentration limit is generally used for the application of the special labelling requirements of Annex II section 2.8 to protect already sensitised individuals. A SDS is required for the mixture containing an ingredient above this concentration.

Note 2: This concentration limit is used to trigger classification of a mixture as a skin sensitizer.

Note 3: This concentration limit is used to trigger classification of a mixture as a respiratory sensitizer.

The evaluation of the spray dilution with the CLP criteria is only accurately possible if information on the entire composition of a plant protection product is available. Ctgb or the company which owns the authorised plant protection product can perform this as they have this confidential information.

An alternative worst-case option could be to:

- take the CLP classification of the plant protection product
- determine the dilution factor of the applied plant protection product (Ctgb spray volume table).
- use the calculation rules of CLP to determine if specific H phrases of the PPP also apply for the diluted plant protection product.

Example:

Nimrod vloeibaar has the following classification: H319 Causes serious eye irritation.

Nimrod vloeibaar is applied on strawberries on a 1liter product per hectare for strawberries in a dilution 500-600 liter water/ha.

This means a spray solution of 0.5%.

The generic cut-off value for serious eye irritation is 1%.

Conclusion: according to the CLP calculation rules to the diluted plant protection product does not have to be classified.

5 Conclusion

The present report presented information and methodologies to answer the three in itself individual questions all related to worker's exposure to residues of plant protection products (PPP) requested by the Dutch Ministry of SZW (Dutch Ministry of Social Affairs and Employment projects).

Provide a methodology to determine the period to enter a PPP-treated crop with gloves for a safe re-entry. Calculate the period to safely re-enter crops (PPERI) with gloves for authorized plant protection products.

For authorisation purposes worker exposure is calculated and must be safe. Worker exposure to PPPs can be mitigated by using gloves. When the risk assessment concludes a need for gloves, they are prescribed on the label of the PPP.

A new methodology was developed to calculate the period for which workers must wear gloves to mitigate risk of residue exposure to a safe level (in this report called PPERI). The PPERI is pesticide and agricultural use specific. The methodology was shown to be suitable to determine the PPERI. Currently there is no PPP and agricultural uses specific PPERI on the label of a plant protection product. The RIVM recommends to include the PPERI calculation into the national authorization process of PPPs, and to include the PPERI calculation into the EU harmonized models for worker exposure calculation. The information on agricultural use specific PPERI can for instance be then placed on the label as part of the authorization procedure. The PPERI will be linked to product, product use and crop. This will improve the ability for employers to ensure the safety of workers.

What is the current view on dermal absorption of dry substances, i.e. worker exposure during re-entry and how relevant is this for approval of PPP's worker scenario?

Currently dermal absorption studies with liquids (product or dilutions) are used as worst-case for the worker safety assessment of PPPs. To refine the worker exposure assessment it was suggested to use DA values from studies with dried residues, since the worker is exposed to dried foliar residue. There is currently no harmonized study protocol available how to perform such a study. The current scientific position on dermal absorption of dried residue was summarized and a new dermal absorption test protocol for dried residues was described in this report. It was concluded that currently additional research and harmonization is required on a European level to refine the worker exposure assessment with dermal absorption studies on dried residue.

Do the spray dilutions of products with toxicological properties like acute toxicity, skin irritation and or sensibilization, keep their properties and for which period? And. Do the foliar residues of products with toxicological properties like acute toxicity, skin irritation and or sensibilization, keep their properties and for which period?

PPPs and active substances in PPPs can have toxic properties, for which in some cases CLP classification is required (e.g. irritation and sensibilization). This classification can result in H phrases and P-phrases (risk mitigating measures) according to CLP legislation. Spray dilutions of PPPs are diluted up to 1000 times. Operators are exposed to the spray dilutions and workers are exposed to the dried foliar residue, which can be considered a concentrated dry spray dilution. It is unclear if the hazard classifications (H-phrases) for acute toxicity, irritation or sensibilization of the PPP or active substance also apply for spray dilutions or dried foliar residue and, if required, for which period gloves are obligatory risk mitigation measures according to CLP. Toxicity studies to determine the acute toxicity, irritation and sensibilization of spray dilutions or dried foliar residue are currently not required for authorization of PPPs. There is no scientific literature available which determines the toxic properties of spray dilutions or dried foliar residue, although some studies report adverse health effects of workers exposed to PPPs. The CLP calculation rules provide a methodology to determine the necessity of classification of a dilution, although all components in the dilution should be known and taken into account. As a worst-case approach, the CLP generic concentration limits can be used to classify the dilution based on the classification of the product. The CLP calculation rules do not apply for dried foliar residue. Finally, it is recommended to further investigate the acute toxicity, irritation and sensibilisation effects of spray dilutions and dried foliar residue from classified PPPs preferably by non-animal testing strategies. Investigation of the toxic properties (acute toxicity, irritation and sensibilisation) of the spray dilutions and dried foliar residue may provide evidence if spray dilutions and dried foliar residue can actually possess these properties, as the acute toxic, irritation and sensibilisation properties of spray dilutions and dried foliar residue is currently still debated.

6 Acknowledgement

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Annex

Annex Table A1

Table A 1: Crop and working task (activity) specific transfer coefficients (TCs) for the three exposure models: EUROPOEM II, EFSA OPEX and U.S. EPA OPPED

EUROPOEM II			EFSA OPEX					U.S. EPA OPPED		
Crop	Activity	TC (cm ² /hr)	Crop	Activity	TC (cm ² /hr) ^A			Crop	Activity	TC (cm ² /hr)
					no work clothing	work clothing	work clothing plus gloves			
vegetables (field)	All	2500	Brassica vegetables, Bulb vegetables, Fruiting vegetables, Leaf vegetables and fresh herbs, Legume vegetables	Reaching, picking	5800	2500	580	Cotton, Beans/Peas Dry	Hand Weeding	70
Strawberries	All	3000	Golf course, turf or other sports lawns	Maintenance	5800	2500	580	Sunflower	Scouting	90

EUROPEM II			EFSA OPEX					U.S. EPA OPPEP		
Fruit (from trees)	All	4500	Low berries and other small fruits	Reaching, picking	5800	3000	750	Peach	Propping	100
Ornamentals	All	5000	Cereals, Grassland and lawns, Hops, Oilseeds, Root and tuber vegetables	Inspection , irrigation	12500	1400	No TC ^B	Almonds	Harvesting Mechanical	190
			Ornamentals	Cutting, sorting, bundling, carrying	14000	5000	1400	Cotton, Tomato Fresh	Scouting	210
			Cane fruit, Citrus fruit, Oilfruits, Pome fruit, Stone fruit, Tree nuts	Searching , reaching, picking	22500	4500	2250	Chrysanthemums	Pinching	230
			Grapes	Hand harvesting	30000	10100	No TC ^B	Nursery Citrus	Pruning	230
								Nursery Citrus	Hand Harvesting	230
								Cauliflower	Scouting	330
								Cucumber, Squash Summer	Hand Harvesting	550
								Olive, apple	Hand Pruning	580

EUROPOEM II	EFSA OPEX	U.S. EPA OPPEP		
		Grapes Table/Raisin	Scouting	640
		Tobacco	Hand Harvesting	800
		Cotton	Harvesting Mechanical	900
		Corn Sweet, Beans/Peas Dry	Scouting	1100
		Strawberry	Hand Harvesting	1100
		Tomato, Fresh	Hand Harvesting	1100
		Tomato, Fresh	Tying	1100/1200
		Blackberries	Hand Harvesting	1200
		Cabbage, Blackberry, Peach, Apple, Orange, Grapefruit	Hand Harvesting	1400
		Potato	Irrigation	1900
		Cotton	Harvesting Mechanical	2400
		Golf Course Turf	Maintenance, greens only	2500
		Apple	Thinning	3600
		Golf Course Turf	Maintenance	3700
		Cauliflower	Scouting	4200
		Cauliflower	Hand Harvesting	4200

EUROPEM II	EFSA OPEX	U.S. EPA OPED	
		Cabbage	Hand Weeding 4200
		Nursery Crops	Hand Harvesting 4800
		Cotton	Harvesting Mechanical 5050
		Grapes Table/Raisin	Hand Harvesting 5500
		Sod	Harvesting 6700
		Sweet Corn Fresh	Hand Harvesting 8800
		Grapes Wine	Hand Harvesting 10100
		Grapes Table/Raisin	Cane Turning 19300

Annex Figure A1

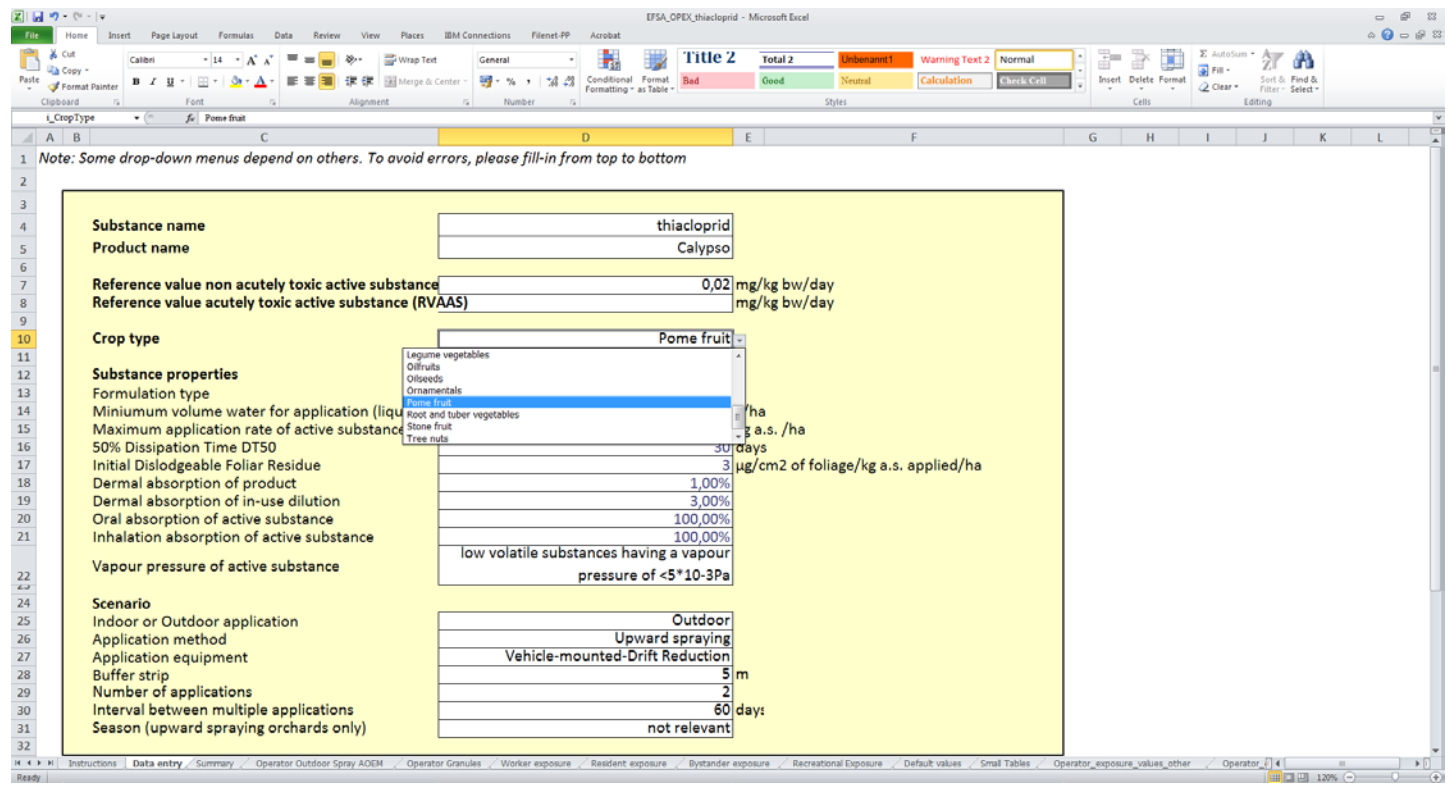


Figure A 1: Screenshot of the EFSA OPEX model, depicting the data entry sheet for simultaneous exposure calculation for Operators, Workers, Residents and Bystander

**Annex Figure A2:
Literature search terms for ii) acute toxicity of dried residues**

Embase Session Results (Embase & Medline)

No.	Query	Results
66		24 (potential) relevant items selected
#14		47 additional items found in Scopus: total:
37		
#13	AND english:la	
66		
#13		
#12	AND [2005-2018]/py	
151		
#12		
#5	AND (#6 OR #7 OR #8 OR #9 OR #10 OR #11)	
208,841		
#11		
	('health effects': ti,ab OR effects: ti OR symptoms: ti,ab) AND complaints: ti,ab OR 'self-reported': ti,ab OR 'health parameters': ti,ab OR intoxication*: ti,ab OR 'occupational exposure': ti OR 'occupational exposure'/mj	
6,279		
#10		
	'inhalation exposure': ti,ab,de OR 'respiratory exposure': ti,ab OR 'skin exposure': ti,ab,de OR 'dermal exposure': ti,ab OR 'eye exposure': ti,ab	
7,752		
#9		
	'contact exposure': ti,ab OR 'short term exposure': ti,ab OR (((exposure OR exposed) NEAR/5 (application OR applicant* OR applicator* OR applying)): ti,ab) OR ((exposure NEAR/3 sprayer*): ti,ab) OR ((exposure NEAR/5 (reentry OR 're entry' OR 're entering' OR reentering)): ti,ab) OR ((exposure NEAR/5 ('withdrawal period*' OR 'waiting period*')): ti,ab)	
107,518		
#8		

'**toxicity period**': ti,ab OR '**toxic period**': ti,ab OR ((**duration** NEAR/3 (**toxicity** OR **toxic**)): ti,ab) OR '**half lives**': ti,ab OR '**half life**': ti,ab OR '**foliar half**': ti,ab OR '**residu* decay**': ti,ab OR '**disappearance rate**': ti,ab OR '**dissipation pattern***': ti,ab OR '**dissipation behavio?r**': ti,ab OR '**dissipation kinetics**': ti,ab OR '**field dissipation**': ti,ab OR **dissipated** OR '**residu* toxicity**': ti,ab OR '**drug half live**': ti,ab,de OR '**half live time**': ti,ab,de OR '**residual concentrations**': ti,ab OR '**residu* limit***': ti,ab OR '**residu* value***': ti,ab OR '**mrl value***': ti,ab OR **mrl**: ti,ab

280,611

#7

'**acute toxicity**'/de OR '**acute poisoning**'/de OR '**toxic dose**'/de OR '**toxic concentration**'/de OR '**intoxication**'/de OR '**skin toxicity**'/de OR '**eye toxicity**'/de OR '**lung toxicity**'/de OR '**toxic inhalation**'/de OR '**eye irritation**'/de OR '**skin irritation**'/de OR '**lung irritation**'/de OR '**irritation**'/de OR '**sensitization**'/de

147,981

#6

((**acute** NEAR/5 (**toxicity** OR **toxic** OR **poisoning**)): ti,ab) OR '**toxic properties**': ti,ab OR '**toxic dose***': ti,ab OR '**toxic concentration***': ti,ab OR '**skin toxicity**': ti,ab OR '**eye toxicity**': ti,ab OR '**respiratory toxicity**': ti,ab OR '**lung toxicity**': ti,ab OR '**eye irritation**': ti,ab OR '**skin irritation**': ti,ab OR '**lung irritation**': ti,ab OR '**respiratory irritation**': ti,ab OR '**toxicity endpoints**': ti,ab OR '**exposure limits**': ti,ab OR **irritation**: ti,ab OR **sensitization**: ti,ab

459

#5

#3 AND #4

3,784

#4

'**foliar residue***': ti,ab OR (**residu***: ti,ab AND **foliar**: ti,ab) OR '**foliar wash-off**': ti,ab OR '**dry residue***': ti,ab OR '**dried residue***': ti,ab OR '**dry substance***': ti,ab OR '**dried substance***': ti,ab OR '**dry film***': ti,ab OR '**dried film***': ti,ab OR '**dry solution***': ti,ab OR '**dried solution***': ti,ab OR '**dried spray**': ti,ab OR '**dried deposit***': ti,ab OR '**dried deposit***': ti,ab OR '**dry deposit***': ti,ab OR '**spray deposit***': ti,ab

333,954

#3

#1 OR #2

316,288

#2

**'plant protection product'/de OR 'pesticide'/exp OR
'herbicide'/exp OR 'insecticide'/exp OR 'fungicide'/exp OR 'wood
protecting agent'/de OR 'rodenticide'/de OR 'agricultural
chemical'/de**

99,303

#1

**'plant protection products': ti,ab OR 'pesticidal agent*': ti,ab OR
pesticide*: ti,ab OR herbicide*: ti,ab OR insecticide*: ti,ab OR
fungicide*: ti,ab OR agrochemicals: ti,ab**

**Annex Figure A2:
Literature search terms for ii) acute toxicity of dried residues**

Embase Session Results (Embase & Medline)

No.	Query	Results
248		96 (potential) relevant items selected 47 additional items found in Scopus: total:
132	#18 #17 AND english:la	
257	#17 #16 AND [2005-2018]/py	
504	#16 #9 AND (#10 OR #11 OR #12 OR #13 OR #14 OR #15)	
208,841	#15 'health effects': ti,ab OR effects: ti OR symptoms: ti,ab OR complaints: ti,ab OR 'self-reported': ti,ab OR 'health parameters': ti,ab OR intoxication*: ti,ab OR 'occupational exposure': ti OR 'occupational exposure'/mj	
167,954	#14 'inhalation exposure'/de OR 'skin exposure'/de	
7,745	#13 'contact exposure': ti,ab OR 'short term exposure': ti,ab OR (((exposure OR exposed) NEAR/5 (application OR applicant* OR applicator* OR applying)): ti,ab) OR ((exposure NEAR/3 sprayer*): ti,ab) OR ((exposure NEAR/5 (reentry OR 're entry' OR 're entering' OR reentering)): ti,ab) OR ((exposure NEAR/5 ('withdrawal period*' OR 'waiting period*')): ti,ab)	
103,907	#12 'toxicity period': ti,ab OR 'toxic period': ti,ab OR ((duration NEAR/3 (toxicity OR toxic)): ti,ab) OR 'half lives': ti,ab OR 'half life': ti,ab OR	

'residu* decay': ti,ab OR **'disappearance rate':** ti,ab OR
'dissipation pattern*': ti,ab OR **'dissipation behavior':** ti,ab OR
'dissipation kinetics': ti,ab OR **'residu* toxicity':** ti,ab OR **'drug half
live':** ti,ab,de OR **'half live time':** ti,ab,de OR **'residual
concentrations':** ti,ab OR **'residu* limit*':** ti,ab OR **'residu*
value*':** ti,ab OR **'mrl value*':** ti,ab OR **mrl:** ti,ab

280,584

#11

'acute toxicity'/de OR **'acute poisoning'/de** OR **'toxic dose'/de** OR
'toxic concentration'/de OR **'intoxication'/de** OR **'skin toxicity'/de**
OR **'eye toxicity'/de** OR **'lung toxicity'/de** OR **'toxic inhalation'/de**
OR **'eye irritation'/de** OR **'skin irritation'/de** OR **'lung irritation'/de**
OR **'irritation'/de** OR **'sensitization'/de**

147,893

#10

((acute NEAR/5 (toxicity OR toxic OR poisoning))): ti,ab) OR **'toxic
properties':** ti,ab OR **'toxic dose*':** ti,ab OR **'toxic
concentration*':** ti,ab OR **'skin toxicity':** ti,ab OR **'eye toxicity':** ti,ab
OR **'respiratory toxicity':** ti,ab OR **'lung toxicity':** ti,ab OR **'eye
irritation':** ti,ab OR **'skin irritation':** ti,ab OR **'lung irritation':** ti,ab
OR **'respiratory irritation':** ti,ab OR **'toxicity endpoints':** ti,ab OR
'exposure limits': ti,ab OR **irritation:** ti,ab OR **sensitization:** ti,ab

1,655

#9

#6 AND (#7 OR #8)

866,049

#8

'horticulture'/exp OR **'greenhouse'/exp** OR **'orchard'/exp** OR
'crop'/exp OR **'crop production'/de** OR **'crop protection'/de** OR
'plant'/exp OR **'leaves'/de** OR **'plant leaf'/de** OR **'leaf surface'/de**
OR **'agricultural workers'/de**

401,024

#7

greenhouse*: ti,ab OR **glasshouse*:** ti,ab OR **horticultur*:** ti,ab OR
orchard*: ti,ab OR **crops:** ti,ab OR **plants:** ti,ab OR **trees:** ti,ab OR
shrubs: ti,ab OR **bushes:** ti,ab OR **leaves:** ti,ab OR **'plant leaf':** ti,ab
OR **'leaf surface':** ti,ab OR **foliar:** ti,ab OR **foliage:** ti,ab OR
'agricultural workers': ti,ab OR **'farm workers':** ti,ab OR
farmers: ti,ab OR **agrochemicals:** ti,ab OR **'pesticide sprayers':** ti,ab

OR **'pesticide applicators'**: ti,ab OR **applicators**: ti,ab OR **'human volunteers'**: ti,ab

5,205

#6

#3 AND (#4 OR #5)

50,177

#5

'dilution'/de OR 'emulsion' OR 'suspension'/de OR 'indoor residual spraying'/de OR 'pesticide spraying'/de

192,493

#4

'diluted solution*': ti,ab OR 'diluted spray*': ti,ab OR 'dilute solution*': ti,ab OR dilution: ti,ab OR 'spray dilution*': ti,ab OR 'spraying dilution*': ti,ab OR 'spray solution*': ti,ab OR 'sprayed solution*': ti,ab OR 'spraying solution*': ti,ab OR 'spray application*': ti,ab OR 'pesticide spraying': ti,ab OR emulsion: ti,ab OR suspension: ti,ab

333,757

#3

#1 OR #2

316,112

#2

'plant protection product'/de OR 'pesticide'/exp OR 'herbicide'/exp OR 'insecticide'/exp OR 'fungicide'/exp OR 'wood protecting agent'/de OR 'rodenticide'/de OR 'agricultural chemical'/de

99,218

#1

'plant protection products': ti,ab OR 'pesticidal agent*': ti,ab OR pesticide*: ti,ab OR herbicide*: ti,ab OR insecticide*: ti,ab OR fungicide*: ti,ab OR agrochemicals: ti,ab

**Annex Figure A4:
Literature search terms for iii) dermal absorption**

Embase Session Results (Embase & Medline)

No.	Query	Results
27		15 (potential) relevant items selected
#10		17 additional items found in Scopus:
total: 32		
#9	AND english:la	
20		
#9		
#8	AND [2005-2018]/py	
61		
#8		
#5	AND (#6 OR #7)	
17,435		
#7		
	'skin absorption'/de OR 'skin penetration'/de OR 'skin permeability'/de OR 'dermal exposure'/de OR 'skin exposure' OR ('absorption'/de AND 'skin'/de)	
8,081		
#6		
	'dermal absorption': ti,ab OR 'skin absorption': ti,ab OR 'cutaneous absorption': ti,ab OR 'dermal exposure': ti,ab OR 'skin exposure': ti,ab OR 'cutaneous exposure': ti,ab OR 'dermal uptake': ti,ab OR 'skin uptake': ti,ab OR 'cutaneous uptake': ti,ab OR 'dermal penetration': ti,ab OR 'skin penetration': ti,ab OR 'cutaneous penetration': ti,ab OR 'dermal permeability': ti,ab OR 'skin permeability': ti,ab OR 'cutaneous permeability': ti,ab OR 'dermal transfer': ti,ab OR 'skin transfer': ti,ab OR 'cutaneous transfer': ti,ab	
5,145		
#5		
#3	AND #4	
8,470		
#4		

'foliar residue*': ti,ab OR (residu*: ti,ab AND foliar: ti,ab) OR 'foliar wash-off': ti,ab OR 'dry residue*': ti,ab OR 'dried residue*': ti,ab OR 'dryed residue*': ti,ab OR 'dried substance*': ti,ab OR 'dryed substance*': ti,ab OR 'dried substance*': ti,ab OR 'dry film*': ti,ab OR 'dryed film*': ti,ab OR 'dried film*': ti,ab OR 'dry solution*': ti,ab OR 'dryed solution*': ti,ab OR 'dryed spray': ti,ab OR 'dried deposit*': ti,ab OR 'dryed deposit*': ti,ab OR 'dry deposit*': ti,ab OR 'spray deposit*': ti,ab OR 'pesticide residue*': ti,ab OR 'herbicide residue': ti,ab

333,954

#3

#1 OR #2

316,288

#2

'plant protection product'/de OR 'pesticide'/exp OR 'herbicide'/exp OR 'insecticide'/exp OR 'fungicide'/exp OR 'wood protecting agent'/de OR 'rodenticide'/de OR 'agricultural chemical'/de

99,303

#1

'plant protection products': ti,ab OR 'pesticidal agent*': ti,ab OR pesticide*: ti,ab OR herbicide*: ti,ab OR insecticide*: ti,ab OR fungicide*: ti,ab OR agrochemicals: ti,ab

