NAM-BASED PHOTOTOXICITY RISK ASSESSMENT FRAMEWORK FOR AGROCHEMICALS

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A proposed NAM-based tiered phototoxicity testing and human risk assessment framework for agrochemicals

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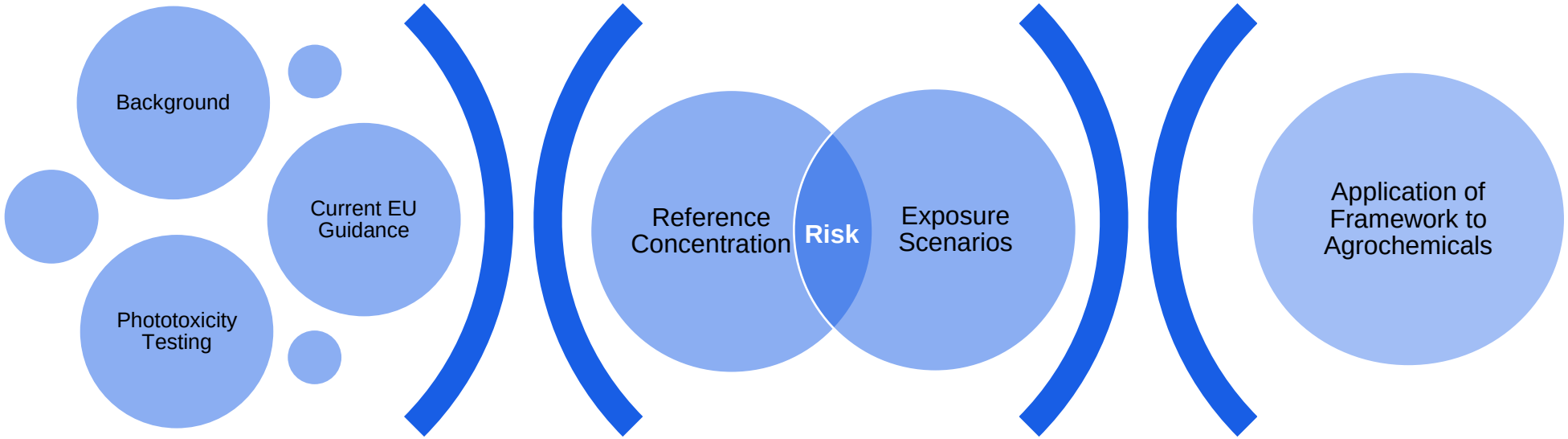
ABSTRACT

Phototoxicity testing is required by European regulations for agrochemicals with UV/visible molar extinction/absorption coefficient (MEC) higher than 10 L x mol^{-1} x cm^{-1} in the 290–700 nm wavelength range. Furthermore, regulations identify a need of considering human exposure in case of positive results. While *in vitro* OECD test guidelines are available for hazard characterisation, there is no guidance on how to utilise positive results in human exposure risk assessments. Our goal was to take a first step towards developing a NAM based tiered testing approach and a framework for non-dietary acute human dermal risk assessment for phototoxicity to agrochemicals. The proposed framework can be divided into a few steps: 1) use the OECD updated MEC values of 1000 L x mol^{-1} x cm^{-1} as trigger for phototoxicity testing; 2) establish a reference concentration (RfC) from *in vitro* phototoxicity studies using BMC approach, 3) estimate potential exposure to skin, target organ for phototoxicity, using EFSA exposure models, product specific labels and skin penetration values, and 4) phototoxicity risk assessment; 5) refinement to RfC and/or exposure estimates can be considered. Finally, case studies of a nematicide and an herbicide active substance are provided to illustrate the proposed framework.

https://www.sciencedirect.com/science/article/abs/pii/S0273230022001374

Discussion Topics



Highlights

- Obsolete trigger value for photosafety assessment of agrochemicals in EU
- Tiered phototoxicity testing approach
- Framework for phototoxicity human risk assessments and refinements
- Establish health-based reference values using *in-vitro* studies only
- Proposed approach to estimate potential skin exposure to agrochemicals
- Case studies to illustrate framework

Risk Assessment Approach

Hazard (Toxicity)

Ability to cause harm/adverse health effect.

Microsoft 365 stock image

H E R

Exposure

Amount of a substance that one can potentially be exposed to.

Credit: Marakele Animal Sanctuary

Risk

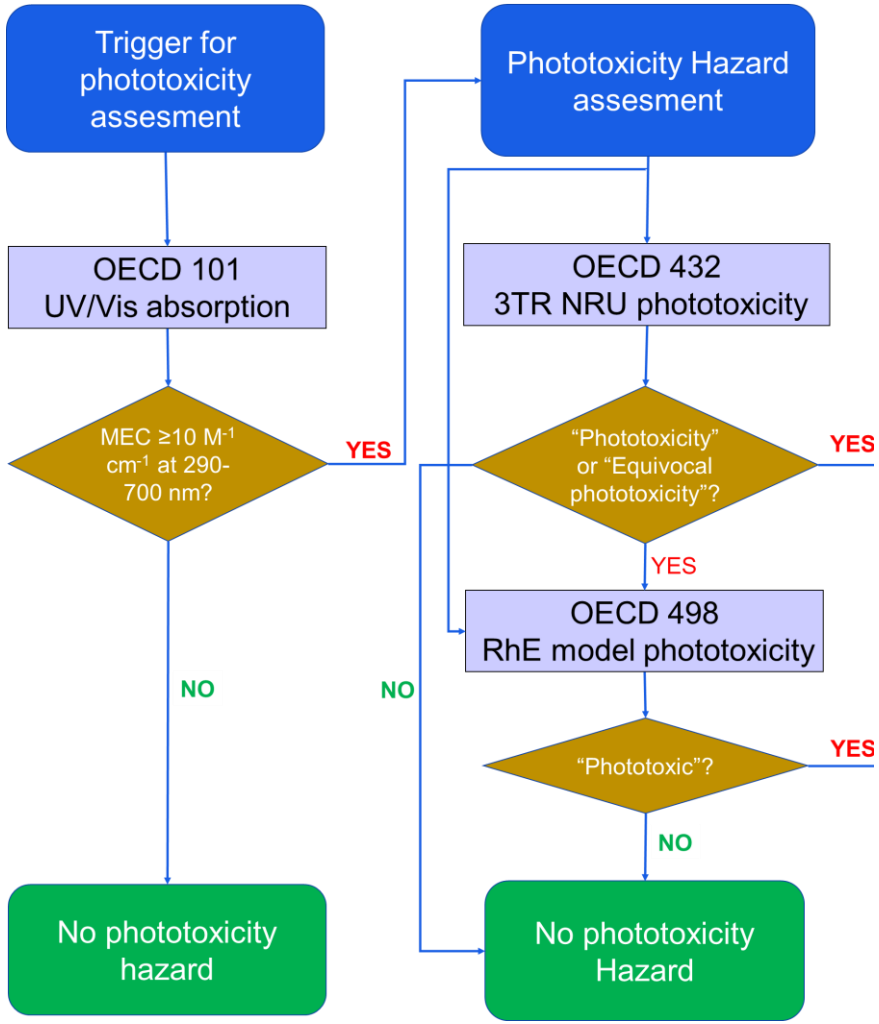
The likelihood that adverse effect will occur under the conditions of product use.

Product label provides risk mitigation options

Current EU Guidance

required where the active substance absorbs electromagnetic radiation in the range 290-700 nm and is liable to reach the eyes or light-exposed areas of skin, either by direct contact or through systemic distribution.

If the UV/Vis molar extinction/absorption coefficient of the active substance is less than 10 L × mol^{-1} × cm^{-1}, no toxicity testing is required



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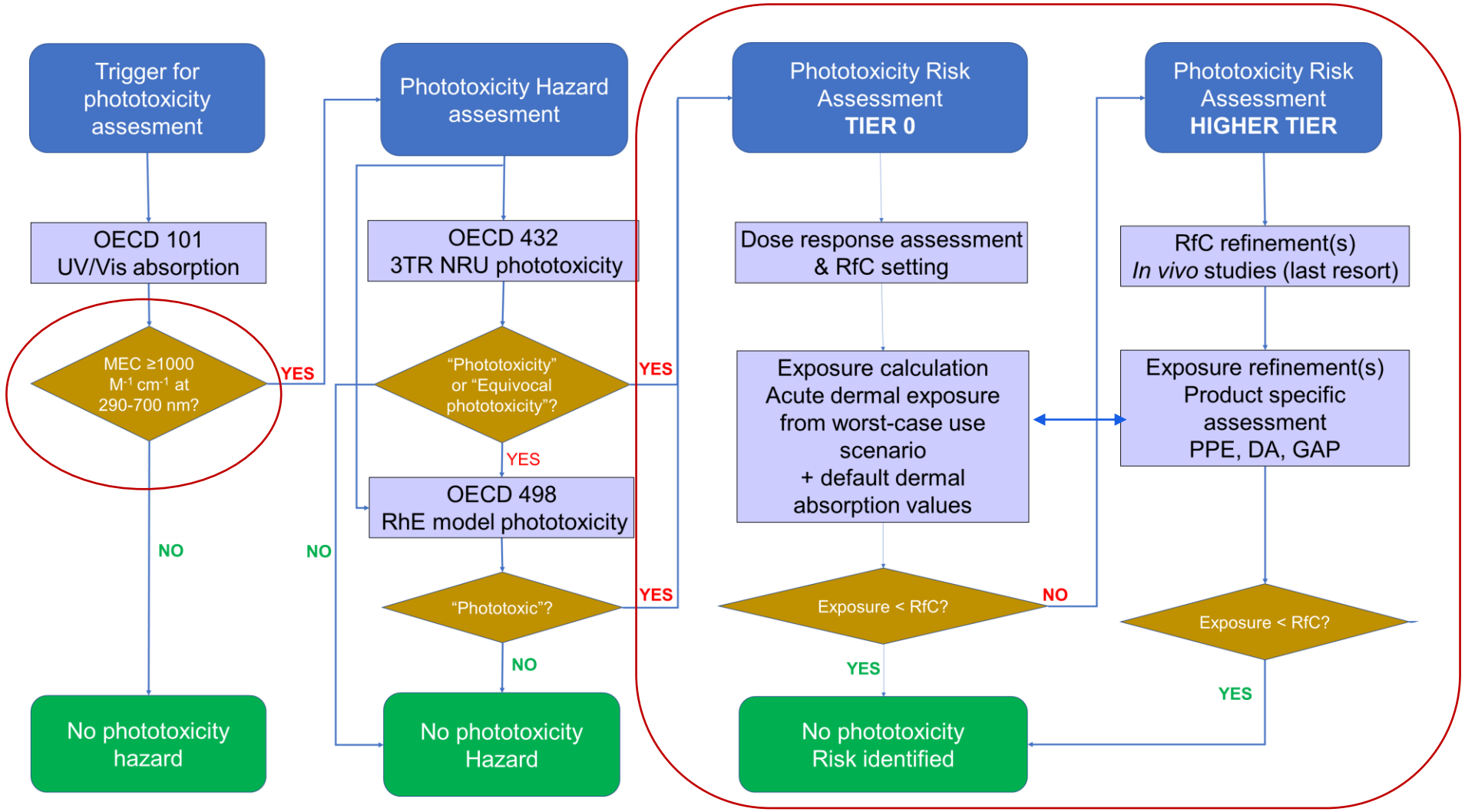
Hazard (Toxicity)

Ability to cause harm/adverse health effect.

"a positive result shall be taken into account when considering potential human exposure"

Proposed Risk Assessment Approach



Proposed Framework for Agrochemicals

1. Use the OECD updated MEC values of 1000 $L.mol^{-1}.cm^{-1}$ as trigger for phototoxicity testing
2. Establish a reference concentration (RfC) from *in vitro* phototoxicity studies using BMC approach
3. Estimate potential exposure to skin, target organ for phototoxicity, using EFSA exposure models, product specific labels and skin penetration values
4. Perform the phototoxicity risk assessment
5. Refine RfC and/or exposure estimates as needed

Proposed Framework

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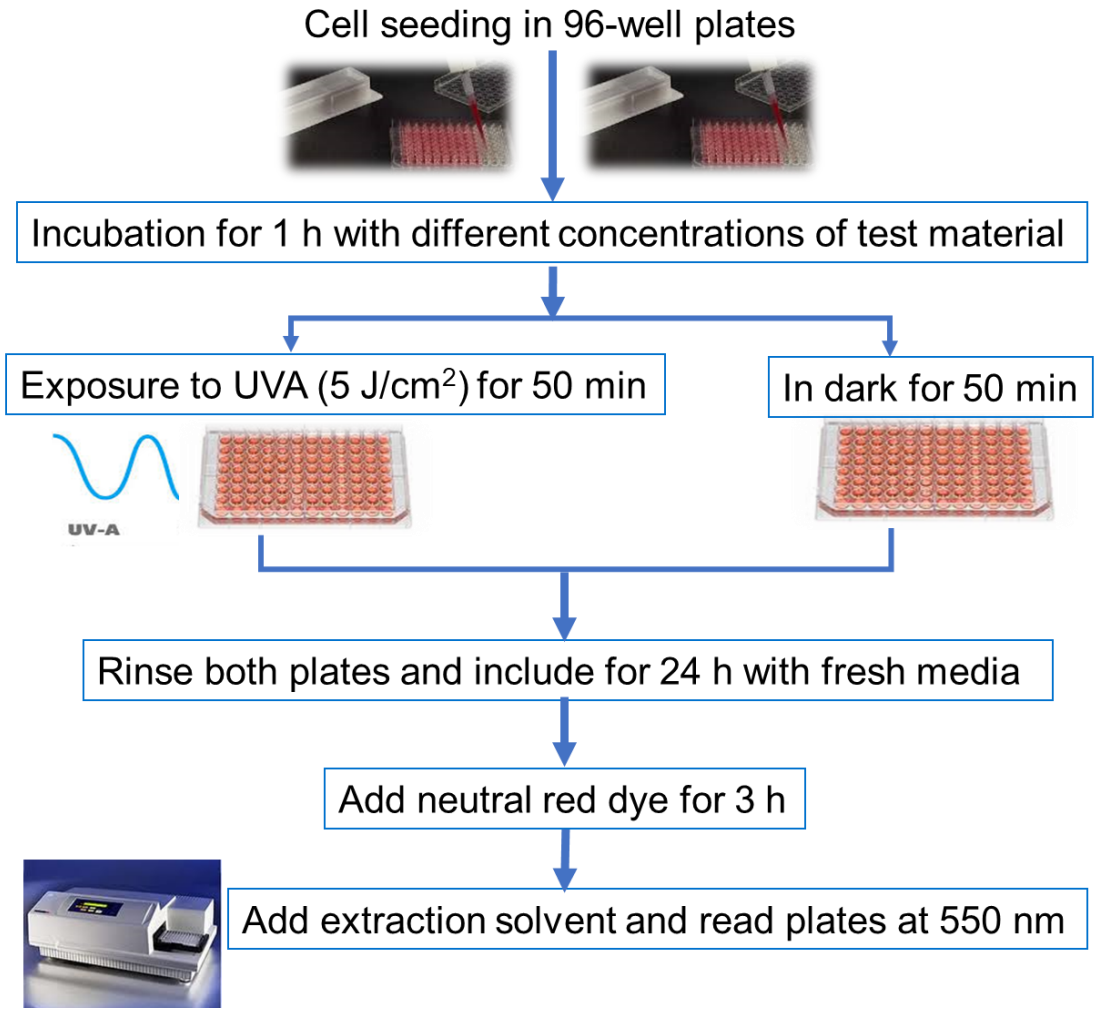
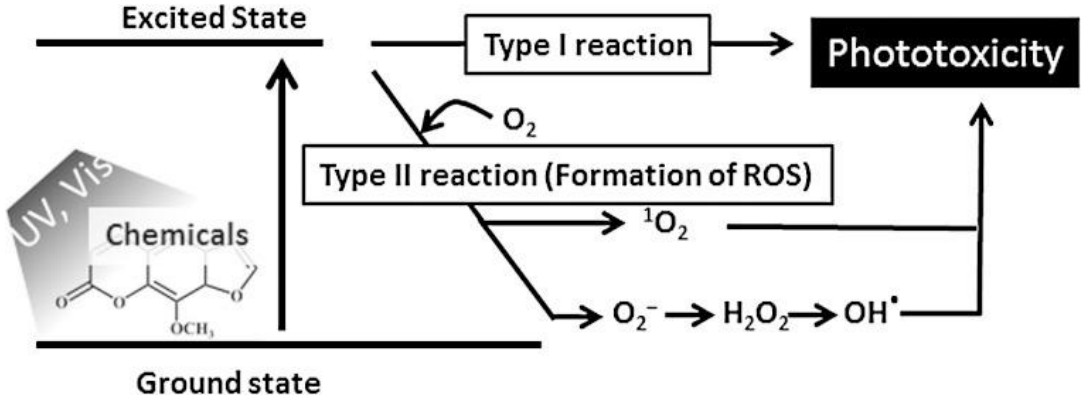
In Vitro Phototoxicity Testing (OECD 432)





The two types of reaction that cause phototoxicity (Adapted from Ibuki & Toyooka, 2014)

Case Study (OECD 432): RfC Setting

Positive for potential phototoxicity (OECD 432), i.e.,20% cytotoxicity in the presence of UVA light

Entire concentration response analyzed using EFSA PROAST tool to establish a Benchmark Concentration (BMC)

BMC analysis	Run #1	Run #2	Mean value
$BMCL_{20}$ (µg/mL)*	11.8	11.8	11.8
$BMCU_{20}$ (µg/mL)	19.6	17.9	18.75

*BMCL being conservative values from a risk assessment point of view and therefore can be considered as a RfC for Tier 0 level

Based on $BMCL_{20}$ of 11.8 µg/mL, calculated RfC for phototoxicity was 3.5 µg/cm^2 (i.e., $BMCL_{20}$*0.3).

Proposed Framework

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Identify Relevant Exposure Scenarios

Acute dermal Exposure

Mixing/loading: concentrate

Application : Spray Dilution

Bystander/Resident: Spray Drift

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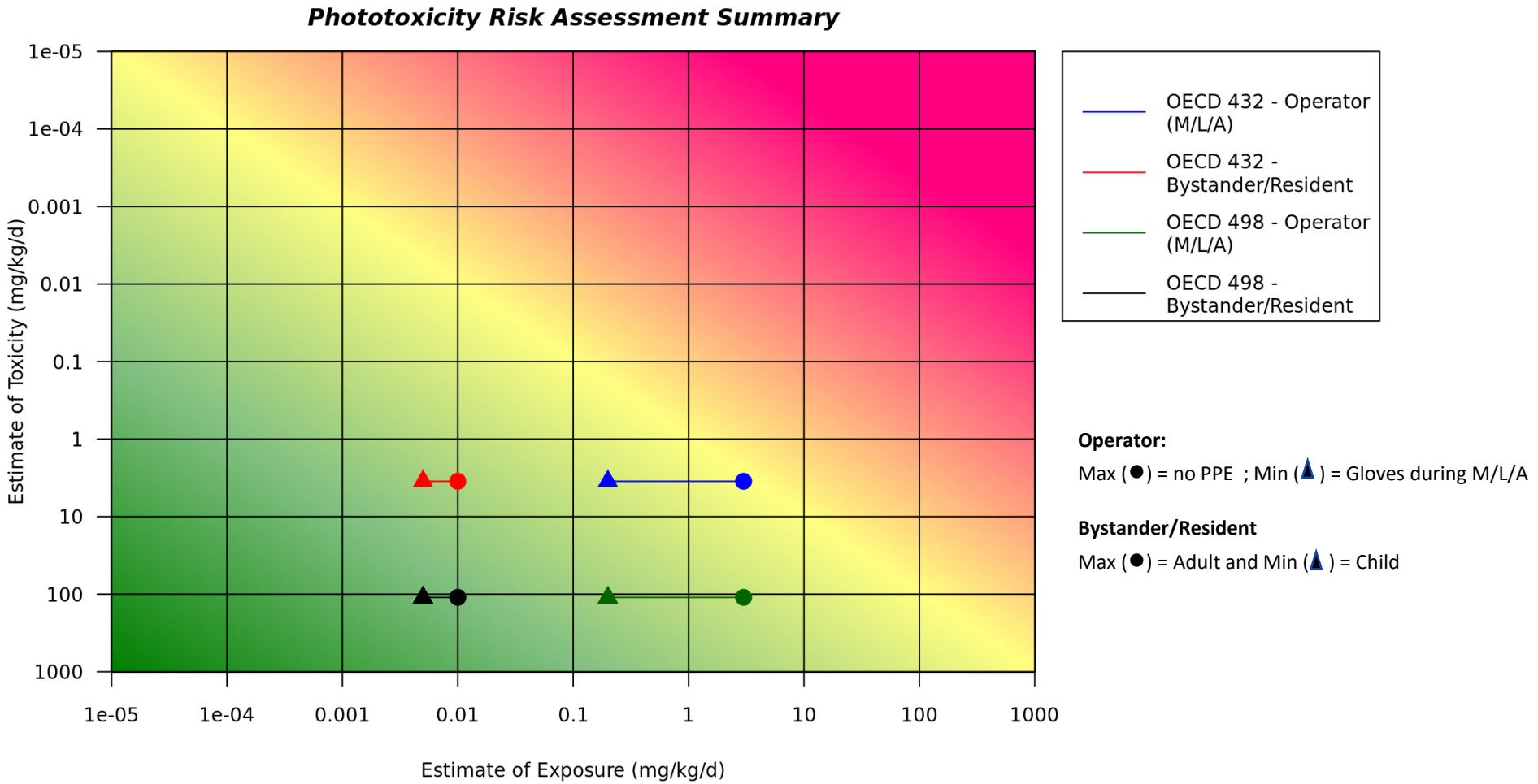
Case Study: Phototoxicity Risk Estimates

Exposure Modelling from EFSA Model (2014)		Operator (M/L/A)[4] M/L (hands)	App (hands)	App (body)	Total	Bystander/Resident[5,6]	
Without PPE[1]	Exposure to skin (µg)	1396	668	295	2359	Child	29
	Exposure to skin per unit area[2] (µg/cm^2)	1.7	0.8	0.02	2.5		0.005
	% RfC[3]	48%	23%	0.5%	72%		0.1%
+ Gloves (M/L/A)	Exposure to skin (µg)	32	134	4	170	Adult	95
	Exposure to skin per unit area[2] (µg/cm^2)	0.04	0.2	0	0.2		0.01
	% RfC[3]	1%	5%	0%	6%		0.3%

[1]Normal work clothing (long-sleeved shirt, long pants, socks, and shoes) but no PPE;
[2]Adjusted for skin surface area based on surface area of hands of an adult = 820 cm^2 and surface area of the body of an adult = 16370 cm^2 (EFSA, 2014).
[3]RfC (µg/cm^2) = $BMCL_{20}$ × 0.3 mL/cm^2
[4]M/L/A = Mixing/Loading/Application
[5]Total dermal exposure from surface deposits & entry into treated crops considered;
[6]Adjusted for skin surface area that could potentially be exposed assuming trunk is covered (i.e., total body surface area minus trunk) child = 5573 cm^2 and adult = 10660 cm^2

OECD 432 vs 498



Operator:

Max (●) = no PPE ; Min (▲) = Gloves during M/L/A

Bystander/Resident

Max (●) = Adult and Min (▲) = Child

Summary

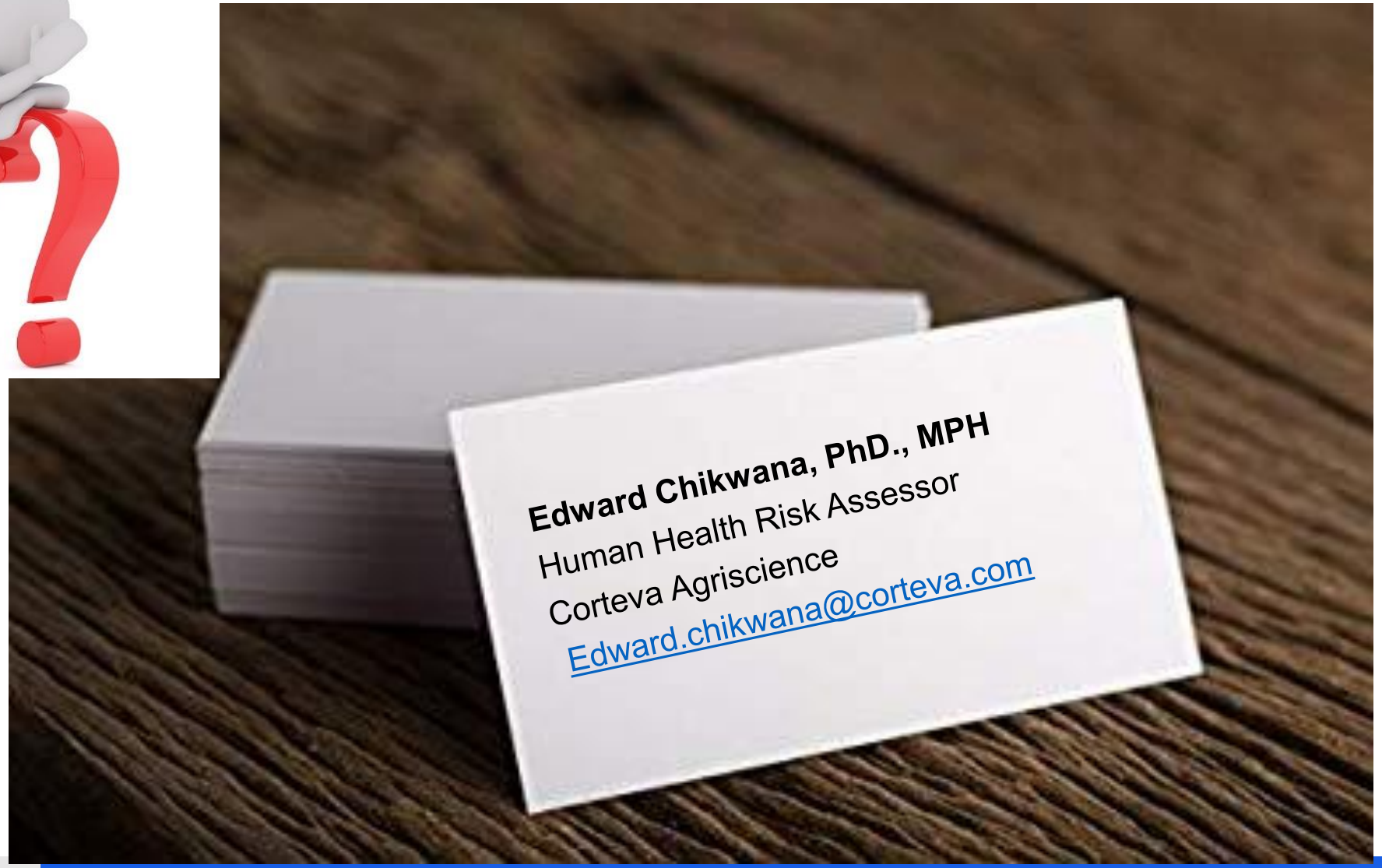
Hazard Identification

- ✓ Use Updated MEC value
- ✓ Determine RfC from in-vitro studies

Exposure Characterization

- ✓ Modeled dermal exposure
- ✓ Dermal penetration refinement

Phototoxicity Risk Characterization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