REGISTRATION REPORT

Part B

Section 6

Mammalian Toxicology

Detailed summary of the risk assessment

Product code: **Nordox 75 WG**

Chemical active substance(s):

Copper (I) oxide (Cu_2O), 750 g/kg

Interzonal

NATIONAL ASSESSMENT

Poland

(Authorization in accordance to Art. 43)

Applicant: Nordox AS

Submission date: 31/01/2022

Evaluation date: December 2022

MS Finalisation date: March 2023

Version history

When	What
31/01/2022	Original version from the applicant Nordox AS for Art. 43 submission. All new data and information are marked in yellow.
12/2022	Version evaluated by zRMS PL
03/2023	Version revised by PL zRMS to take into account comments of cMS

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Submission and Evaluation of Copper compounds under Art.43 of 1107/2009

General observation: Deviation from standard Guidance Documents and EFSA conclusion is necessary and unavoidable for Copper.

The RMS and EFSA are held to assess plant protection products according to the existing methodology described in a series of guidance documents (GDs). Those have been developed for synthetic, organic molecules, and are in most cases not applicable to minerals and Copper. This has led to an EFSA conclusion that indicated a number of critical concerns, or assessments that could not be finalized, which do not reflect any realistic risk, but rather illustrate the inappropriateness of the current GDs for the assessment of Copper. This can easily be seen in a number of endpoints that suggest a high risk exists at concentrations below natural background of this essential micronutrient. **This has been recognized by EFSA, the RMS and several MS (see comments from DE and IT in the Peer review Report), and the EU Commission has mandated EFSA with the development with a Copper specific guidance (Mandate No. 2019-0036).**
Art.43 submissions and their evaluation by MS are unfortunately due before this GD will be available. The current EFSA conclusion and list of endpoints could at best be considered as a first tier, and applicants as well as MS are required to deviate from the standard procedures described in the GD for the following reasons:

- The current GD do not consider bio-availability; for an essential, ubiquitous micronutrient that is a metal it is indispensable to provide assessment methodologies that consider the bioavailability and the potentially toxic fraction in each real-world exposure scenario. Total concentrations do not result in any meaningful outcome.
- Data normalisation to enable comparison of toxicological lab and field data as well as data obtained with different bioavailable fractions is a pre-requisite to allow a realistic assessment of potential risk. Simplistic worst-case scenarios will always indicate a high risk already at naturally occurring concentrations.
- For a homeostatically tight controlled essential element the application of assessment factors is meaningless. The question whether an excess exposure or deficiency leads to an adverse disruption of the homeostatic control cannot be approached in this way. Further, the exceptional data richness of the Copper dossier and more than 100 years of experience with the use as fungicide make safety factors unnecessary.

These unique features of Copper are already considered in the assessment of Copper under separate legislation (REACH, BPD). While COM directed EFSA in their mandate to take advantage of those methodologies, TF members have to anticipate their use and in their proposed assessments of the critical areas of concern identified in the EFSA conclusion. This should be reviewed once the new GD is available and no use should be cancelled until then.

Submission and Evaluation of Copper compounds under Art.43 of 1107/2009

General observation: Copper compounds should not be considered as Candidate for Substitution (CfS).

The implementing Regulation (EU) 2018/1981 is renewing the approval of the active substance Copper compounds as candidate for substitution (CfS), in accordance with Regulation (EC) 1107/2009. Whereas (12) considers that Copper compounds are persistent and toxic in accordance with points 3.7.2.1 and 3.7.2.3 of Annex II to Regulation (EC) 1107/2009 (PBT assessment), and fulfil the condition set in the second indent of point 4 of Annex II to Regulation (EC) 1107/2009.

The EUCuTF disagrees with the approval as CfS. The conditions in Annex to Regulation (EC) 1107/2009 lack the exemption of inorganic compounds like Copper minerals from the PBT assessment as it has been established under other chemical legislations like REACh and BPD. As laid down in those legislations, the term persistence is meaningless for an element or mineral, due to its natural occurrence. Persistence per se is therefore not a relevant parameter and consequently a PBT assessment is not carried out for inorganic compounds under REACh and BPD. The recent mandate from COM to EFSA directs the development of a guidance towards methods and procedures available under those legislations better adapted for the assessment of inorganic compounds, where the relevant parameter is their bioavailability. This should include an exempt statement regarding the PBT assessment to harmonize the assessment of the same compounds under different legislations.

It should be noted that persistence of minerals is considered not relevant for being categorized as low-risk active substance according to Regulation (EU) 2017/1432. This is clearly not compatible with the same parameter leading to a classification as CfS under the same Regulation (EC) 1107/2009.

The EUCuTF is of the opinion that Copper compounds should not be considered CfS, and have lodged an action for annulment against Regulation (EU) 2018/1981 and renewing the approval of the active substance Copper compounds as candidate for substitution (case number T-153/19 European Union Task Force v. European Commission).

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on Nordox 75 WG*

Product name and code	Nordox 75 WG
Formulation type	Water dispersible granule [Code: WG]
Active substance(s) (incl. content)	Copper (I) oxide; 750 g/kg
Function	Fungicide and bactericide
Product already evaluated as the 'representative formulation' during the approval of the active substance(s)	Yes
Product previously evaluated in another MS according to Uniform Principles	Greece (authorization number: 60765 / Re-approval date: 17.12.2018) France (authorization number: 2010130 / First date of approval: 13.10.2003) France (authorization number: 2110180 / First date of approval: 30.11.2011) Spain (authorization number: 22560 / Re-approval date: 14.11.2018) Portugal (authorization number: APV3468 / Year of approval: 2003) Italy (authorization number: 10632 / Re-approval date: 30.01.2019)

* Information on the detailed composition of Nordox 75 WG can be found in the confidential dRR Part C.

Justified proposals for classification and labelling

According to the criteria given in Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008, the following classification and labelling with regard to toxicological data is proposed for the preparation:

Table 6.1-2: Justified proposals for classification and labelling for Nordox 75 WG according to Regulation (EC) No 1272/2008

Hazard class(es), categories	Aquatic Acute 1 Aquatic Chronic 2
Hazard pictograms or Code(s) for hazard pictogram(s)	GHS09
Signal word	Warning
Hazard statement(s)	H410 – very toxic to aquatic life with long lasting effects
Precautionary statement(s)	P273 P501
Additional labelling phrases	To avoid risks to man and the environment, comply with the instructions for use. [EUH401]

Table 6.1-3: Summary of risk assessment for operators, workers, residents and bystanders for Nordox 75 WG

	Result	PPE / Risk mitigation measures
Operators	Acceptable	None
Workers	Acceptable	None
Residents	Acceptable	None
Bystanders	Acceptable	None

No unacceptable risk for operators, workers, residents and bystanders was identified when the product is used as intended. No specific PPE is necessary.

A summary of the critical uses and the overall conclusion regarding exposure for operators, workers and residents/bystanders is presented in the following table.

Table 6.1-4 Critical uses and overall conclusion of exposure assessment

(dermal absorption of copper: concentrate – 0.1%, dilution 1%)

1	2	3	4	5	6	7	8	9	10			
Use-No.	Crops and situation (e.g. growth stage of crop)	F, Fn, Fpn G, Gn, Gpn or I **	Application		Application rate		PHI (d)	Remarks: (e.g. safener/synergist (L/ha)) critical gap for operator, worker, resident or bystander exposure based on [Exposure model]	Acceptability of exposure assessment			
			Method / Kind (incl. application technique ***)	Max. number (min. interval between applications) a) per use b) per crop/ season	Max. application rate kg as/ha	Water L/ha min / max			Operator	Worker	Residents	Bystander
4	Strawberry	G	LC	3 (7)	1.0	200	3	Operators (Dutch greenhouse model) Workers (EFSA-OPEX model)	A	A	n/a	n/a

1	2	3	4	5	6	7	8	9	10			
5	Tomato Eggplant Pepper	G	LC	3 (7)	1.0	200	10	Operators (Dutch greenhouse model) Workers (EFSA-OPEX model)	A	A	n/a	n/a
7	Lettuce, scarole	G	LC	3 (7)	1.0	300	3	Operators (Dutch greenhouse model) Workers (EFSA-OPEX model)	A	A	n/a	n/a
8	Cucumber	G	LC	3 (7)	1.0	200	3	Operators (Dutch greenhouse model) Workers (EFSA-OPEX model)	A	A	n/a	n/a

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1
** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application
*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held
n/a - not applicable

Explanation for column 10 "Acceptability of exposure assessment"

A	Exposure acceptable without PPE / risk mitigation measures	
R	Further refinement and/or risk mitigation measures required	
N	Exposure not acceptable/ Evaluation not possible	

Table 6.1-5 Critical uses and overall conclusion of exposure assessment

(assuming dermal absorption of copper: concentrate – 1%, dilution 9%)

1	2	3	4	5	6	7	8	9	10			
Use-No.	**Crops and situation (e.g. growth stage of crop)**	**F, Fn, Fpn G, Gn, Gpn or I ****	**Application**		**Application rate**		**PHI (d)**	**Remarks:** **(e.g. safener/synergist (L/ha))** **critical gap for operator, worker, resident or bystander exposure based on [Exposure model]**	**Acceptability of exposure assessment**			
			Method / Kind **(incl. application technique *****	**Max. number (min. interval between applications)** **a) per use** **b) per crop/ season**	**Max. application rate kg as/ha**	**Water L/ha** **min / max**			**Operator**	**Worker**	**Residents**	**Bystander**
4	Strawberry	G	LC	3 (7)	1.0	200	3	Operators (Dutch greenhouse model) Workers (EFSA-OPEX model)	R	R	n/a	n/a
5	Tomato Eggplant Pepper	G	LC	3 (7)	1.0	200	10	Operators (Dutch greenhouse model) Workers (EFSA-OPEX model)	R	R	n/a	n/a
7	Lettuce, scarole	G	LC	3 (7)	1.0	300	3	Operators (Dutch greenhouse model) Workers (EFSA-OPEX model)	R	R	n/a	n/a

1	2	3	4	5	6	7	8	9	10			
8	Cucumber	G	LC	3 (7)	1.0	200	3	Operators (Dutch greenhouse model) Workers (EFSA-OPEX model)	R	R	n/a	n/a

* Use number(s) in accordance with the list of all intended GAPs in Part B, Section 0 should be given in column 1
** F: professional field use, Fn: non-professional field use, Fpn: professional and non-professional field use, G: professional greenhouse use, Gn: non-professional greenhouse use, Gpn: professional and non-professional greenhouse use, I: indoor application
*** e.g. LC: low crops, HC: high crop, TM: tractor-mounted, HH: hand-held
n/a - not applicable

Explanation for column 10 "Acceptability of exposure assessment"

A	Exposure acceptable without PPE / risk mitigation measures	
R	Further refinement and/or risk mitigation measures required	
N	Exposure not acceptable/ Evaluation not possible	

Data gaps

Data gaps should be listed in the summary to give an overview (especially for cMS).

Noticed data gaps are: None

6.2 Toxicological Information on Active Substance(s)

Information regarding classification of the active substances and on EU endpoints and critical areas of concern identified during the EU review are given in Table 6.2-1.

Table 6.2-1: Information on active substance

	Copper(I) oxide
Common Name	Cuprous oxide
CAS-No.	1317-39-1
Classification and proposed labelling	
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	Acute oral Cat. 4 Acute inhalation Cat. 4 Eye irritation Cat. 1 H302: Harmful if swallowed H332: Harmful if inhaled H318: Causes serious eye damage
Additional C&L proposal	None
Agreed EU endpoints	
AOEL systemic	0.08 mg/kg bw/d (based on human data)
Reference	EFSA Conclusion, 2018
Conditions to take into account/critical areas of concern with regard to toxicology	
According to EFSA Conclusion for active substance	Risks to vineyard workers

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for Nordox 75 WG is given in the following tables. Full summaries of studies on the product that have not been previously considered within an EU peer review process are described in detail in Appendix 2.

The following tests were performed on Nordox 75 WG: acute LD_{50} oral (rat), acute LD_{50} dermal (rat), acute LC_{50} inhalation (rat), skin irritation (rabbit), eye irritation (rabbit) and sensitization of the skin (maximisation test on guinea pig). Nordox 75 WG was a representative formulation in the EU review of Copper compounds. The acute toxicity studies for Nordox 75 WG were evaluated during the review and were considered adequate. Thus, the studies are not described in detail in this document.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for Nordox 75 WG

Type of test, species, model system (Guideline)	Result	Acceptability	Classification (acc. to the criteria in Reg. 1272/2008)	Reference
LD_{50} oral, rat (OECD 401)	3165 mg/kg bw	Yes	None	xxx (2000) EU agreed dRAR, Vol.3, B6 (2016)
LD_{50} dermal, rat (OECD 402)	> 2000 mg/kg bw	Yes	None	xxx (2000) EU agreed dRAR, Vol.3, B6 (2016)
LC_{50} inhalation, rat (OECD 403)	> 5 mg/L air	Yes	None	xxx (2000) EU agreed dRAR, Vol.3, B6 (2016)
Skin irritation, rabbit (OECD 404)	Non-irritant	Yes	None	xxx (2000) EU agreed dRAR, Vol.3, B6 (2016)
Eye irritation, rabbits (US EPA equivalent to EC method B5)	Non-irritant	Yes	None	xxx (1999) EU agreed dRAR, Vol.3, B6 (2016)
Skin sensitisation, guinea pig (OECD 406, M&K)	Non-sensitising	Yes	None	xxx (2000) EU agreed dRAR, Vol.3, B6 (2016)
Supplementary studies for combinations of plant protection products	No data – not required			

Table 6.3-2: Additional toxicological information relevant for classification/labelling of Nordox 75 WG

	Substance (concentration in product, % w/w)	Classification of the substance (acc. to the criteria in Reg. 1272/2008)	Reference	Classification of product (acc. to the criteria in Reg. 1272/2008)
Toxicological properties of active substance(s) (relevant for classification of product)	Copper (I) oxide (85% (w/w))	Acute oral Cat.4 (H302) Acute inhalation Cat.4 (H332) Eye irritation Cat.1 (H318)	EFSA Journal 2018;16(1)5152	None
Toxicological properties of non-active substance(s) (relevant for classification of product)	Confidential information, please refer to Part C			
Further toxicological information	Confidential information, please refer to Part C			

6.4 Toxicological Evaluation of Groundwater Metabolites

Copper is an element and therefore the formation of metabolites or breakdown products is not possible.

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substance in Nordox 75 WG are presented in the following table.

Table 6.5-1: Dermal absorption rates for active substances in Nordox 75 WG

	Copper	
	Value	Reference
Concentrate	0.1 %	xxx (2016, 2020) New studies reported in Appendix 2
Dilution	1 % (Dilution factor 1:1500)	xxx (2016, 2020) New studies reported in Appendix 2
Concentrate	1 %	Appendix A - List of end points for the active substance and the representative formulation. EFSA (European Food Safety Authority), 2018. Conclusion on the peer review of the pesticide risk assessment of the active substance copper compounds. EFSA Journal 2018;16(1):5152, 119 pp.
Dilution	9 %	

zRMS:
Dermal absorption values of copper (as Copper (I) oxide) from a product Nordox 75 WG determined in this registration report according to the Triple pack' approach derived based on acceptable studies and

interpreted in line with current EU guidelines is used for risk assessment are: 0.1% for the concentrate and 1% for the dilution. Since Triple pack' approach is valid for determination of dermal absorption to be used for health risk according to EU Guidance on dermal absorption (EFSA Journal 2017;15(6):4873) therefore these endpoints were used for exposure and risk assessment.

On the other hand it is noted that in Conclusion on the peer review of the pesticide risk assessment of the active substance copper compounds. EFSA Journal 2018;16(1):5152, 119 pp "*Appendix A - List of end points for the active substance and the representative formulation"* it is recommended to use as default values of dermal absorption of copper of 1% from the concentrated products and 9% from dilution (0.33g Cu/L). The detailed information how these values were derived is not provided in this document. However, it is noted that the absorption values proposed in EFSA Journal 2018;16(1):5152, 119 pp "*Appendix A - List of end points for the active substance and the representative formulation"* can only be obtained if residues of Cu in the pooled tape strips and in the stripped skin found in *in vitro studies* are taken as absorbable which is highly improbable noting that inorganic compounds of copper are not water soluble and not lipid soluble, and they form solid residues when a spray droplets dried up on leaves surface.
As pointed out by xxx (2020) (KCP 7.3/04) such high dermal absorption could only be possible if all residues of Cu in the pooled tape strips and in the stripped skin in *in vitro* studies will be absorbed into blood, which is rather not probable for insoluble inorganic copper compounds . In the *in vivo* study in rats (**KCP 7.3/03)** the amount of the applied dose of ^{65}CU in the stripped skin was very low; the largest amount being observed in dilution II (0.3%) at 24 hours. The amount present in the stratum corneum showed no clear decrease over time and the majority remained in the upper layers. For all 3 dose levels the amount of ^{65}Cu located in the stratum corneum was not available for absorption under the conditions of the study(**KCP 7.3/03)**. For these reasons RMS do not consider that these values of dermal absorption of copper of 1% from the concentrated products and 9% from dilution as over conservative should be used for exposure and risk assessment, however the relevant calculation were done for comparative purposes.

6.5.1 Justification for proposed values - Copper

~~The proposed dermal absorption rates for Copper are based on dermal absorption studies on a formulation containing Copper hydroxide. The study results are summarised in the following table.~~
Full summaries of studies on the dermal absorption of Copper **that have not previously been evaluated** within an EU peer review process are described in detail in Appendix 2.
It has already been established during the EU peer review that, given the nature of the active substance (Cu^{2+}), dermal penetration factors for both concentrate and in-use spray dilutions from these studies are justifiably relevant to all forms of Copper (oxide, hydroxide, oxychloride, tribasic sulphate and Bordeaux Mixture) and all formulation types (WP, WG, and SC). Therefore, the results of the studies below are relevant for Nordox 75 WG.

zRMS:
The dermal absorption values used for estimation exposure were derived in Triple pack' approach based on studies presented in Appendix A 2.10 and in EFSA Journal 2018;16(1):5152, 119 pp "*Appendix A - List of end points for the active substance and the representative formulation"*

Table 6.5-2: Summary of the results of submitted dermal absorption studies for Copper

Test	Concentrate	Spray dilution (dilution factor)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	0.39% for the neat formulation (350 g/kg)	2.8% for the intermediate dose (3 g/L) 7.5% for the low dose (0.3 g/L)	53.8WG (DPX-GFJ52 (35% as metallic copper)	Yes	See point A.2.10	Yes	KCP 7.3/01 xxx (2016)
In vitro (rat)	2.6% for the neat formulation (350 g/kg)	3.6% for the intermediate dose (3 g/L) 14% for the low dose (0.3 g/L)	53.8WG (DPX-GFJ52 (35% as metallic copper)	Yes	See point A.2.10	Yes	KCP 7.3/02. xxx (2016)
In vivo (rat	<0.051% for the neat formulation (350 g/kg	not determined	53.8WG (DPX-GFJ52 (35% as metallic copper)	Yes	See point A.2.10	Yes	KCP 7.3/03 xxx (2016)
In vitro (human)	0.1 %	0.5 % (1:1500)	SPU-08740-F Copper hydroxide 50 WP)	Supplementary	~~Yes (see Appendix A 2.10)~~ No (study not provided in Appendix A 2.10)	Justification not accepted. Endpoint cannot be used for current product.	xxx, 2018
In vitro (human)	0.4 %	9 % (0.3g Cu/L)	• DPX-GFJ52 (Copper hydroxide 53.8WG)	Supplementary	~~Yes (see Appendix A 2.10)~~ No (study not provided in Appendix A 2.10)	Justification not accepted. Endpoint cannot be used for current product.	xxx, 2017*
In vitro (human)	0.6 % 0.1 %	8.9 % 3.5 %	• Copper hydroxide 50 WP. • Flowbrix	Supplementary	~~Yes (see Appendix A 2.10)~~ No (study not provided in Appendix A 2.10)	Justification not accepted. Endpoint cannot be used for current product.	xxx, 2015*

Test	Concentrate	Spray dilution (dilution factor)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference*
In vitro (human)	0.09 %	5.68 % (1.5 g/L)	• Copper hydroxide 250 g Cu/L, SC. • Copper hydroxide 50 WP • H1B10 Copper hydroxide 25% WG • Copper Oxychloride 37.5 NC WG • Flowbrix • Bordeaux mixture 20% Cu WP • BBC/Bouillie Bordelaise • Nordox 75 WG	Supplementary	~~Yes (see Appendix A 2.10)~~ No (study not provided in Appendix A 2.10)	Justification not accepted. Endpoint cannot be used for current product.	xxx, 2012*

* indicates that a study was reviewed at EU level

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

Table 6.6-1: Product information and toxicological reference values used for exposure assessment

Product name and code	Nordox 75 WG
Formulation type	WG
Category	Fungicide and bactericide
Active substance(s) (incl. content)	**Copper** 750 g/kg
AOEL systemic	0.08 mg/kg bw/d
Inhalation absorption	100 %
Oral absorption	50 %
Dermal absorption	Concentrate: 0.1 % Dilution: 1.0 % (1:1500 dilution)

6.6.1 Selection of critical use(s) and justification

The critical GAP used for the exposure assessment of the plant protection product is shown in Table 6.1-4.

A list of all intended uses within the zone is given in Part B, Section 0.

6.6.2 Operator exposure (KCP 7.2.1)

6.6.2.1 Estimation of operator exposure

A summary of the exposure models used for estimation of operator exposure to the active substances during application of Nordox 75 WG according to the critical use(s) is presented in Table 6.6-2. The outcome of the estimation is presented in Table 6.6-3 (acute exposure) and Table 6.6-4 (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-2: Exposure models for intended uses

Critical use(s)	Strawberry: 1.0 kg a.s./ha Fruiting vegetables: 1.0 kg a.s./ha Leaf vegetables: 1.0 kg a.s./ha
Model(s)	Dutch greenhouse model (Van Golstein Brouwers, Y.G.C., Marquart, J. and Van Hemmen, J.J. (1996))

Table 6.6-3: Estimated operator exposure (acute exposure)

An AAOEL was not allocated during the peer review for the renewal of approval of Copper (EFSA, 2017). Therefore, estimates of the acute exposure to operators has not been conducted.

Table 6.6-4: Estimated operator exposure (longer term exposure)

(dermal absorption: concentrate – 0.1%, dilution 1%)

Model data	Level of personal protective equipment	Operator exposure [mg/kg bw/day]	% of systemic AOEL
Application rate 1.0 kg a.s./ha, spraying in greenhouse			
Dutch greenhouse model 1 ha/day 70 kg bodyweight	Potential exposure	--	54

The risks posed to operators from the application of Nordox 75 WG are considered to be acceptable.

Table 6.6-5A: Estimated operator exposure (longer term exposure)

(dermal absorption: concentrate –1%, dilution 9%)

Model data	Level of personal protective equipment	Operator exposure [mg/kg bw/day]	% of systemic AOEL
Application rate 1.0 kg a.s./ha, spraying in greenhouse			
Dutch greenhouse model 1 ha/day 70 kg bodyweight	Potential exposure	--	339
Dutch greenhouse model 1 ha/day 70 kg bodyweight	Protective gloves +coverall	--	50

The risks posed to operators wearing coverall and protective gloves from the application of Nordox 75 WG are considered to be acceptable.

zRMS:
Dermal absorption of copper (as copper (I) oxide) from a product Nordox 75 WG determined in this registration report according to the Triple pack' approach based on acceptable studies and interpreted in line with current EU guidelines to be used for risk assessment are: 0.1% for the concentrate and 1% for the dilution. This approach is considered valid for determination of dermal absorption in case of this application of Nordox 75 WG therefore these endpoints are used for exposure estimation

Taking into account dermal absorption 0.1% for concentrate and 1% for dilution the potential exposures to copper (as copper (I) oxide), estimated with Dutch greenhouse model, of operator applying Nordox 75 WG in the greenhouse on strawberry, tomato, eggplant, pepper, lettuce, scarole or cucumber at rate of 1.0 kg a.s./ha, downward spraying, are all below AOEL, thus these applications do not cause unacceptable risk for operator for not wearing any PPE. In case operator is wearing work wear covering arms, body legs and protective gloves the exposure and risk are lower.

When the higher dermal absorption of 1% from concentrate and 9% from the dilution 9%) is assumed then the exposure of operator is below AOEL for all these applications foreseen in GAP only when operator is wearing work wear covering arms, body and legs during mixing/loading and application and protective gloves during mixing/loading.

6.6.2.2 Measurement of operator exposure

Since the operator exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and consideration of the above mentioned personal protective equipment (PPE), a study to provide measurements of operator exposure was not necessary and was therefore not performed.

6.6.3 Worker exposure (KCP 7.2.3)

6.6.3.1 Estimation of worker exposure

Table 6.6-6 shows the exposure model(s) used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with Nordox 75 WG according to the critical use(s). The outcome of the estimation is presented in Table 6.6-7 (acute exposure) and Table 6.6-8 to **Błąd! Nie można odnaleźć źródła odwołania.** (longer term exposure). Detailed calculations are in Appendix 3.

Table 6.6-6: Exposure models for intended uses

Critical use(s)	Strawberry: 3 x 1.0 kg a.s./ha Fruiting vegetables: 3 x 1.0 kg a.s./ha Leaf vegetables: 3 x 1.0 kg a.s./ha
Model	Guidance on the assessment of exposure of operators, workers, residents and bystanders in risk assessment for plant protection products; EFSA Journal 2014;12(10):3874 calculator version: 30/03/2015

Table 6.6-7: Estimated worker exposure (acute exposure)

An AAOEL was not allocated during the peer review for the renewal of approval of Copper (EFSA, 2017). Therefore, estimates of the acute exposure to workers has not been conducted.

Table 6.6-8: Estimated worker exposure (longer term exposure) for the professional uses – default values

(dermal absorption: concentrate – 0.1%, dilution 1%)

Model data	Level of PPE	Total absorbed dose [mg/kg bw/day]	% of systemic AOEL
Strawberry, application rate 3 x 1.0 kg a.s./ha			
AOEM Model Reaching, picking/Indoor Work rate: 8 hours/day DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha	**Potential** TC: 5800 cm²/person/h	0.0597238	74.65
	Work wear (arms, body and legs covered) TC: 3000 cm²/person/h	0.0308916	38.61
	Work wear (arms, body and legs covered) **and gloves** TC: 750 cm²/person/h	0.0077229	9.65
Fruiting vegetables, application rate 3 x 1.0 kg a.s./ha			
AOEM Model Reaching, picking/Indoor Work rate: 8 hours/day DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha	**Potential** TC: 5800 cm²/person/h	0.0597238	74.65
	Work wear (arms, body and legs covered) TC: 2500 cm²/person/h	0.0257430	32.18
	Work wear (arms, body and legs covered) **and gloves** TC: 580 cm²/person/h	0.0059724	7.47
Leaf vegetables, application rate 3 x 1.0 kg a.s./ha			
AOEM Model Reaching, picking/Indoor Work rate: 8 hours/day DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha	**Potential** TC: 5800 cm²/person/h	0.0597238	74.65
	Work wear (arms, body and legs covered) TC: 2500 cm²/person/h	0.0257430	32.18
	Work wear (arms, body and legs covered) **and gloves** TC: 580 cm²/person/h	0.0059724	7.47

The risks posed to workers re-entering areas treated with Nordox 75 WG are considered to be acceptable.

Table 6.6-9: Estimated worker exposure (longer term exposure) for the professional uses – default values

(dermal absorption: concentrate –1%, dilution 9%)

Model data	Level of PPE	Total absorbed dose [mg/kg bw/day]	% of systemic AOEL
Strawberry, application rate 3 x 1.0 kg a.s./ha			
AOEM Model Reaching, picking/Indoor Work rate: 8 hours/day DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha	**Potential** TC: 5800 cm²/person/h	0.5375143	671.89
	Work wear (arms, body and legs covered) TC: 3000 cm²/person/h	0.2780246	347.53
	Work wear (arms, body and legs covered) **and gloves** TC: 750 cm²/person/h	0.0695051	86.88
Fruiting vegetables, application rate 3 x 1.0 kg a.s./ha			
AOEM Model Reaching, picking/Indoor Work rate: 8 hours/day DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha	**Potential** TC: 5800 cm²/person/h	0.5375142	671.89
	Work wear (arms, body and legs covered) TC: 2500 cm²/person/h	0.2316872	289.61
	Work wear (arms, body and legs covered) **and gloves** TC: 580 cm²/person/h	0.0537514	67.19
Leaf vegetables, application rate 3 x 1.0 kg a.s./ha			
AOEM Model Reaching, picking/Indoor Work rate: 8 hours/day DT_{50}: 30 days DFR: 3 µg/cm²/kg a.s./ha	**Potential** TC: 5800 cm²/person/h	0.5375142	671.89
	Work wear (arms, body and legs covered) TC: 2500 cm²/person/h	0.2316872	289.61
	Work wear (arms, body and legs covered) **and gloves** TC: 580 cm²/person/h	0.0537514	67.19

The risks posed to workers re-entering areas treated with Nordox 75 WG are considered to be acceptable.

6.6.3.2 Refinement of generic DFR value (KCP 7.2)

Not relevant.

6.6.3.3 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under normal conditions of intended uses and considering the above-mentioned PPE, a study to provide measurements of worker exposure is not necessary and was therefore not performed.

zRMS:
Taking into account the dermal absorption 0.1% for concentrate and 1% for dilution the potential exposures

to copper (as copper (I) oxide), of worker entering for 8 hour for various tasks a greenhouse with crops treated with Nordox 75 WG as foreseen in GAP (strawberry, tomato, eggplant, pepper, lettuce, scarole or cucumber at rate of 1.0 kg a.s./ha) estimated with EFSA AOEM model are all below AOEL. Thus these applications do not cause unacceptable risk for worker entering greenhouse for 8 hours to performed various tasks on treated plants. In case the worker is wearing workwear and protective gloves the exposure and risk is further reduced

When the higher dermal absorption is assumed of 1% from concentrate and 9% from the dilution 9%) then the exposure of worker, estimated with EFSA AOEM model, to copper (as copper (I) oxide) is only below AOEL when worker is wearing a work wear covering arms, body and legs and protective gloves and is entering a greenhouse with strawberry, tomato, eggplant, pepper, lettuce, scarole or cucumber treated with Nordox 75 WG at application rate 3 x 1.0 kg a.s./ha, downward spraying. Therefore the risk of workers wearing a workwear covering arms, body and legs and protective gloves is acceptable.

6.6.4 Resident and bystander exposure (KCP 7.2.2)

6.6.4.1 Estimation of resident and bystander exposure

Calculation needs to be conducted only for field uses, since bystanders and residents should not be affected by application in greenhouses. Therefore, no risk assessment is conducted.

6.6.4.2 Measurement of resident and/or bystander exposure

Not relevant.

6.6.5 Combined exposure

Not relevant. The product contains only one active substance.

Appendix 1 Lists of data considered in support of the evaluation

List of data submitted by the applicant and relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 7.3/01	xxx	2016	*In vitro* percutaneous absorption of copper, formulated as Copper Hydroxide (DPX-GFJ52) 53.8WG (35% as metallic copper), through human skin Du-Pont-42821 xxx, The Netherlands GLP: Y Unpublished	N	EUCuTF
KCP 7.3/02	xxx	2016	*In vitro* percutaneous absorption of copper, formulated as Copper Hydroxide (DPX-GFJ52) 53.8WG (35% as metallic copper), through rat skin Du-Pont-42649 xxx, The Netherlands GLP: Y Unpublished	N	EUCuTF
KCP 7.3/03	xxx	2016	*In vivo* percutaneous absorption of copper, formulated as Copper Hydroxide (DPX-GFJ52) 53.8WG (35% as metallic copper), in rats xxx-42648 xxx, The Netherlands GLP: Y Unpublished	N	EUCuTF

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 7.3/04	xxx	2020	The fate of test item residues in the skin membranes in *in vitro* dermal absoprion studies; impact on the risk assesssment of inorganic copper salts n.a. xxx GLP: N Unpublished	N	EUCuTF

List of data submitted or referred to by the applicant and relied on, but already evaluated at EU peer review

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 6.3	xxx	2000	Cobre Nordox 75 WG acute oral toxicity study in the rat 7671/T/082/2000 GLP: Y Unublished	Y	Nordox
KCP 6.3	xxx	2000	Nordox Super 75 WG: acute dermal toxicity (limit test) in the rat 148/024 GLP: Y Unublished	Y	Nordox
KCP 6.3	xxx	2000	Nordox Super 75 WG: acute inhalation toxicity (nose only) study in rat 148/025 GLP: Y Unublished	Y	Nordox

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 6.3	xxx	2000	Nordox Super 75 WG: acute dermal irritation test in the rabbit 148/026 GLP: Y Unublished	Y	Nordox
KCP 6.3	xxx	1999	Nordox 75 DF: Primary eye irritation 6886 GLP: Y Unublished	Y	Nordox
KCP 6.3	xxx	2000	Nordox Super 75 WG: Magnusson and Kligman maximisation study in the guinea pig 148/027 GLP: Y Unublished	Y	Nordox
KCP 7.2/01	xxx	2013	Checking the distribution quality of agrochemicals in the vineyard through the use of field monitoring - xxx, Italy GLP: No Published (Acta. Hort. **978,** p237-243)	N	-
KCP 7.3/05	xxx	2012	*In vitro* dermal absorption of Copper (Cu) from 8 formulations through human skin 9062 xxx, The Netherlands GLP: Y Unublished	N	EUCuTF
KCP 7.3/06	xxx	2015	*In vitro* percutaneous absorption of Copper, formulated as Copper hydroxide 50 WP or Copper oxychloride SC, through human and rat skin V20600/19 Triskelion, The Netherlands GLP: Y Unpublished	N	EUCuTF

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Verte-brate study Y/N	Owner
KCP 7.3/07	xxx	2017	*In vitro* percutaneous absorption of Copper, formulated as Copper Hydroxide (DPX-GFJ52) 53.8 WG (35% as metallic Copper), through human skin V20600/08 xxx, The Netherlands GLP: Y Unpublished	N	EUCuTF
KCP 7.3/08	xxx	2017	Dermal absorption of Copper compounds, a critical analysis N/A EUCuTF GLP: N Unpublished	N	EUCuTF

The following tables are to be completed by MS

List of data submitted by the applicant and not relied on

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner

List of data relied on not submitted by the applicant but necessary for evaluation

Data point	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
KCP XX	Author	YYYY	Title Company Report N Source GLP/non GLP/GEP/non GEP Published/Unpublished	Y/N	Owner

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Not relevant.

A 2.2 Acute oral toxicity (KCP 7.1.1)

Not relevant for Nordox 75 WG because it was the representative for the EU evaluation.

A 2.3 Acute percutaneous (dermal) toxicity (KCP 7.1.2)

Not relevant for Nordox 75 WG because it was the representative for the EU evaluation.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

Not relevant for Nordox 75 WG because it was the representative for the EU evaluation.

A 2.5 Skin irritation (KCP 7.1.4)

Not relevant for Nordox 75 WG because it was the representative for the EU evaluation.

A 2.6 Eye irritation (KCP 7.1.5)

Not relevant for Nordox 75 WG because it was the representative for the EU evaluation.

A 2.7 Skin sensitisation (KCP 7.1.6)

Not relevant for Nordox 75 WG because it was the representative for the EU evaluation.

A 2.8 Supplementary studies for combinations of plant protection products (KCP 7.1.7)

None.

A 2.9 Data on co-formulants (KCP 7.4)

A 2.9.1 Material safety data sheet for each co-formulant

Information regarding material safety data sheets of the co-formulants can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.9.2 Available toxicological data for each co-formulant

Available toxicological data for each co-formulant can be found in the confidential dossier of this submission (Registration Report - Part C).

A 2.10 Studies on dermal absorption (KCP 7.3)

Given the inherent properties of Copper, the penetration of Cu^{2+} ions across the dermis of human skin is independent of the different forms of the active substance (e.g Copper hydroxide, tribasic Copper sulphate, Bordeaux Mixture, Copper oxychloride or Copper oxide) or of the formulation type (WG, WP or SC) applied to the dermis. This principle was accepted during the review of the renewal of approval of Copper. The study below uses a formulation containing Copper hydroxide and can be taken as representative for all formulations containing the forms of Copper supported for the EU approval by the EUCuTF. Please note that it is not appropriate to use the data below as surrogate data for formulations containing a form of Copper that differs from the five forms that was supported during the renewal of approval of Copper.

A 2.10.1 Dermal absorption, in vitro using human skin

Comments of zRMS:	There are three studies of copper dermal absorption presented in this report: *In vitro* percutaneous absorption of copper, formulated as copper hydroxide 53.8WG (DPX-GFJ52 (35% as metallic copper) through human skin (xxx., 2016) KCP 7.3/01 *In vitro* percutaneous absorption of copper, formulated as copper hydroxide 53.8WG (DPX-GFJ52 (35% as metallic copper) through rat skin (xxx, 2016) KCP 7.3/02 *In vivo* percutaneous absorption of copper, formulated as copper hydroxide 53.8WG (DPX-GFJ52 (35% as metallic copper) in rats (xxx, 2016) KCP 7.3/03 All these studies were performed in line with relevant OECD guidelines and in GLP conditions and are acceptable. The mean percentage of ^{65}Copper hydroxide in the WG 53.8 formulation that was considered to be potentially absorbable from the neat formulation was 0.39%, while from spray dilution (0.3 g/L) 7.5 % . It is noted that ca. 99.9% of potentially absorbable copper was found in the pooled tape strips 3+ 15 and in the stripped skin, while less than 0.01% of the applied doses were in the receptor fluid and receptor chamber wash, in which in some case the amount of copper was below LoQ KCP 7.3/01). The mean percentage of potentially absorbable of copper^{65} through rat skin in vitro from the concentrate (350 g/kg) was 2.6 % and from spray dilution (0.3 g/L) 14.0 % (KCP 7.3/02). It is noted again that majority of absorbable copper was found in the in the pooled tape strips 3+ 15 and in the stripped skin, while in total 0.0261% of the applied dose as the concentrate or 4.8442% of the applied dose as spray dilution (0.3g/L) were found respectively in the receptor fluid and receptor chamber wash. Dermal absorption of copper through rat skin in vivo for the concentrate (350 g/kg) was < 0.0521 % and for spray dilution (0.3 g/L) was not possible to determine due to high levels of background endogenous copper in the matrices (KCP 7.3/03), therefore a worst-case value of 1.9% representing the mean missing recovery was used for calculation of dermal absorption in the triple pack approach, which is extremely conservative approach.

	In accordance with the EU guidelines (EFSA Journal 2017;15(6):4873) the Triple pack' approach has been used to estimate dermal absorption of copper to be used for regulatory purpose. The existing in vivo data in rats (KCP 7.3/03) were corrected for the ratio of dermal absorption between in vitro through rat skin (KCP 7.3/02) and through human skin (KCP 7.3/01) according to the following formula. *In vivo human % absorption = in vivo rat % absorption/in vitro rat % absorption x in vitro % human absorption* *Dermal absorption from Concentrate:* = < 0.0521 %/2.6% x 0.39% = < 0.008% *Dermal absorption from the highest dilution = 1.9%/14.0% x 7.5% = 1.0%* According to the Triple pack' approach based on available data a dermal absorption for the highest dilution through human skin to be used for risk assessment was < 0.008% for the concentrate and 1.0 % for the dilution. In the analysis of existing studies on dermal penetration of inorganic copper from the copper-containing agrochemical formulation xxx (2020) (KCP 7.3/04), the researcher who performed or participated in many of these studies pointed out that it questionable whether Cu retained in upper layers of skin are absorbable to blood and further on notes that: -"*no notable absorption into the receptor fluid was observed following the application of various copper-containing agrochemical to human skin in vitro."* -*" Despite slightly raised skin levels of copper following repeated application, still no absorption into the receptor fluid occurred."* -*"A rat in vivo study using ^{65}Cu , that studied the absorption of copper until 144h, again confirmed that no absorption of copper into blood occurs following application of a Copper hydroxide-containing concentrate formulation, while absorption from the diluted product (i.e. 1.9%) could only be, very conservatively, estimated based on the "missing" recovery."* Dermal penetration by Cu inorganic compounds which are not lipophilic and not soluble in water do not have any specific driving force which would induced a movement of Cu from the outer surface of the skin into the circulatory system, eventually leading to systemic exposure towards Cu, therefore it is doubtful whether Cu retained in the pooled tape strips and in the stripped skin will be absorbed into blood. In a way it has been confirmed in the *in vivo* study of dermal absorption in rats in which no notable dermal absorption was noted. In the opinion of xxx (2020) (KCP 7.3/04) based on a generally accepted triple-pack-approach, a dermal absorption value of 0.1% for the concentrate and 1% for diluted products containing inorganic copper compounds , is considered adequately worst case. zRMS concurs with this opinion which is in agreement with the data presented in the submitted studies.

Reference	**KCP 7.3/01**
Report	*In vitro* percutaneous absorption of copper, formulated as Copper Hydroxide (DPX-GFJ52) 53.8WG (35% as metallic copper), through human skin xxx (2016) Du-Pont-42821
Guideline(s)	OECD 428 (2004); OECD Assessment No 28, (2004); EFSA Panel on Plant

	Protection Products and their Residues (PPR): Guidance on Dermal Absorption (2017)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	Not relevant

Material and methods:

Human skin: Source: xxx
Number and sex: 4 female donors.
Anatomical region: Abdomen and/or breast.
Thickness: Dermatomed to 200 to 400 µm.

Test Material:

Non-radiolabeled: Copper hydroxide

Radiolabeled: ^{65}Copper hydroxide

Formulation: The formulation used in this experiment was Copper hydroxide 53.8 WG containing nominal 53.8% ^{65}Copper hydroxide (equivalent to 35% metallic copper).
It was used at three nominal concentrations of copper hydroxide: neat (317 ± 17 g/kg) with 2 spray dilutions of 3 g ^{65}Copper. L^{-1} and 0.3 g ^{65}Copper. L^{-1}.

Test system: A flow-through diffusion cell system (Perm Gear Inc., Riegelsville, PA, USA) was used to study the absorption of the test substance. Approximately 20 h prior to exposure, the split-thickness skin membranes were placed in the 9 mm flow through automated diffusion cells to hydrate the skin. The skin surface temperature was set at 32 ± 1˚C and the humidity was ambient. Following application of the test preparations, the actual temperature was recorded at 15-minute intervals during the study in a diffusion cell containing a non-exposed skin membrane. The receptor fluid was pumped at a speed of approximately 1.2 $mL.h^{-1}$ and consisted of Phosphate buffered saline (PBS) containing 0.01% sodium azide (w/v), supplemented with 6% polyoxy-ethylene 20-oleyl glycol (PEG) (w/v), pH 7.2.
In the flow through cells used the volume of receptor fluid in the receptor chamber beneath the skin was approximately 0.2 mL. At a flow rate of 1.2 $mL.h^{-1}$, this volume was replenished continuously (6 times/hour) such that the rate of diffusion into the receptor fluid did not become a rate limiting step.

Skin integrity: After placing the skin membranes in the diffusion cells, membrane integrity was assessed. 200 µL saline (containing 0.01% sodium azide) and titrated water was applied in the donor compartment of the flow through diffusion cells. The compartment was covered with a glass slide. Samples of the receptor fluid (approx. 1.8 mL/hour) were collected every hour up to three hours following application and measured for radioactivity using liquid scintillation counting

(LSC). Titrated water remaining at the application site was removed and the skin dried with cotton swabs. Membranes were stored overnight to allow wash-out.
Membranes with a permeability coefficient (K_p) for water less that 2.5 x 10^{-3} $cm.h^{-1}$ were taken forward for use in the study.
Skin membranes from one donor for dilution II did not meet the integrity criteria; therefore, exposure to skin samples from a second donor was performed one week later.

Treatment: The undiluted concentrate (powder) was distributed over the skin and wetted using a minimal volume of artificial sweat (to mimic conditions on the skin under occlusive clothing conditions).
For the dilutions, the dose preparations were applied to the split-thickness skin sample with a pipette at the rate of approximately 10 µL/cm^2 exposed skin.
The exposure period was 6-hours for all skin preparations.

Sampling: 24-hours following application, the mass balance was determined, which comprised measurements from the receptor fluid, skin wash, receptor compartment wash, donor compartment wash, pooled tape strips and stripped skin.
Receptor fluid samples were collected at 0-1, 1-2, 2-4, 4-6, 6-12- and 12-24-hours following application. Following 6-hours' exposure, the unabsorbed test substance was removed with mild soap and cotton swabs and dried. A second skin wash was similarly performed at 24-hours post-application and the diffusion cell was dismantled (receptor and donor compartments were washed with ethanol and water).
Each skin membrane was tape stripped 15 times (unless epidermis rupture occurred). Tape strips were pooled as 1, 2, 3, 4, 5, 6-10 and 11-15. Following tape stripping the membranes were collected and stored until analysis.

Radioassay: The amounts of radioactivity in the membrane integrity test samples were determined by liquid scintillation counting (LSC).
The amount of copper was determined at mass 65 m/z and mass 63 m/z using a double focusing high resolution inductively coupled plasma spectrometry (HR-ICP-MS) in medium mode (resolution, 40000) in all collected samples.

Results:
Copper was demonstrated to be sufficiently soluble in the receptor fluid to avoid any risk of back diffusion.

Measurements of the homogeneity of the three concentrations of formulation applied indicated that it was acceptable.

Mean recovery was above 95% in all cases, being approximately 107% for the concentrate (350 g/kg) and both spray dilutions (3 and 0.3 g/L). Therefore, no adjustments for low recovery were required.

The study results are presented in the following Tables:

Distribution of radioactivity at 24 hours after dose application of ^{65}Copper hydroxide in a WG 53.8 formulation (undiluted concentrate) to human skin samples (All cells).

	Distribution of radioactivity (% dose applied)								N= 8 K N° = 0.84
Donor N°	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	
Sex	F	F	F	F	F	F	F	F	
Cell N°	A-1	A-2	A-3	A-4	A-5	A-6	A-7	A-8	MEAN±SD
Skin wash 6h	97.2	96.0	87.9	108.7	110.4	101.7	128.3	114.8	105.6±12.7
Skin wash 24h	0.6	0.4	0.4	0.1	0.2	0.3	0.1	0.1	0.3±0.2
Tape strip 1	0.84	0.42	0.10	0.06	0.42	0.73	0.04	0.05	0.33±0.32
Tape strip 2	0.09	0.06	0.03	0.02	0.11	0.06	0.02	0.02	0.05±0.04
Total tape strips 1 + 2	0.93	0.48	0.13	0.08	0.53	0.79	0.06	0.07	0.38±0.35
Donor chamber	0.16	0.04	0.37	0.01	0.11	0.10	0.01	0.00	0.101±0.124
TOTAL NON-ABSORBED	**98.89**	**96.92**	**88.8**	**108.89**	**111.24**	**102.89**	**128.47**	**114.97**	**106.38±12.30**
Stripped skin	0.36	0.19	<0.00	0.00	0.33	0.30	0.04	0.04	0.16±0.15
Tape strip 3	0.03	0.02	0.00	0.01	0.05	0.03	0.01	0.02	0.02±0.01
Tape strip 4	0.01	0.01	0.00	0.00	0.03	0.01	--	--	0.01±0.01
Tape strip 5	0.02	0.01	<0.00	<0.00	0.02	0.01	--	--	0.01±0.01
Tape strip 6-10	--	0.06	0.01	<0.00	0.05	0.05	--	--	0.03±0.03
Tape strip 11-15	--	--	<0.00	<0.00	0.05	0.01	--	--	0.02±0.02
TOTAL Tape strips 3+ [a]	0.06	0.1	0.01	0.01	0.2	0.07	0.01	0.02	0.07±0.07
TOTAL DOSE SITE	**0.78**	**0.48**	**0.01**	**0.01**	**0.91**	**0.68**	**0.09**	**0.1**	**0.22±0.21**
Receptor fluid (0 - 12h)	0.0008	0.0006	0.0011	<0.0006	<0.0008	0.0007	0.0067	<0.0006	0.0015±0.0021
Receptor fluid (0 - 24h)	<0.0013	<0.0011	0.0023	<0.011	0.0023	0.0013	0.0073	<0.0011	0.0022±0.0021
%Ratio receptor 12h/24h	61	55	48	5	35	54	92	55	**68**
Receptor chamber wash	0.000	0.000	<0.000	<0.000	0.000	<0.000	<0.000	<0.000	<0.00±0.00
TOTAL DIRECT	**0.0021**	**0.0017**	**0.0034**	**0.0116**	**0.0031**	**0.002**	**0.014**	**0.0017**	**0.0050±0.0049**
POTENTIAL (dose site+ receptor)	**0.7821**	**0.4817**	**0.0134**	**0.0216**	**0.9131**	**0.682**	**0.104**	**0.1017**	**0.3875±0.3710**
POTENTIAL (skin+ receptor)	0.3621	0.1917	0.0034	0.0116	0.3331	0.302	0.054	0.0417	0.1625±0.1529
TOTAL RECOVERY	**99.6721**	**97.4017**	**88.8134**	**108.9116**	**112.1531**	**103.572**	**128.574**	**115.0717**	**106.771±12.240**

Evaluation according to EFSA Guidance	
Absorption >75% within half of study duration?	No. (include tape strip values except 1 &2)
Recovery <95%?	No
Total % Potentially Absorbable adjusted according to EFSA (2017)	0.22 ± 0.21 = 0.22 + 0.1764 (k=0.84) **= 0.39%**
[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.	

Distribution of radioactivity at 24 hours after dose application of ^{65}Copper hydroxide in a WG 53.8 formulation (Dilution I) to human skin samples (All cells).

	Distribution of radioactivity (% dose applied)								N= 8 K N° = 0.84
Donor N°	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	
Sex	F	F	F	F	F	F	F	F	
Cell N°	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	MEAN±SD
Skin wash 6h	80.7	99.9	102.4	108.2	99.2	106.8	126.2	102.9	103.3±12.5
Skin wash 24h	2.0	1.5	0.4	1.9	1.3	1.1	2.5	1.5	1.5±0.6
Tape strip 1	0.12	<0.11	<0.11	0.31	<0.11	<0.11	0.48	0.20	0.19±0.14
Tape strip 2	<0.11	<0.11	<0.11	<0.11	<0.11	<0.11	0.45	<0.12	<0.15±0.12
Total tape strips 1 + 2	0.23	0.22	0.22	0.42	0.22	0.22	0.93	0.32	0.35±0.25
Donor chamber	0.03	0.02	0.03	0.19	0.03	0.02	0.05	0.04	0.05±0.06
TOTAL NON-ABSORBED	**82.96**	**101.64**	**103.05**	**110.71**	**100.75**	**108.14**	**129.68**	**104.76**	**105.21±12.93**
Stripped skin	4.2	2.0	<0.1	0.2	0.7	1.2	1.1	0.6	1.3±1.3
Tape strip 3	<0.11	<0.11	<0.11	<0.11	<0.11	<0.11	0.14	<0.12	<0.11±0.01
Tape strip 4	<0.11	<0.11	<0.11	<0.11	<0.11	<0.11	0.26	<0.12	<0.13±0.05
Tape strip 5	<0.11	<0.11	<0.11	<0.11	<0.11	<0.11	0.14	<0.12	<0.11±0.01
Tape strip 6-10	--	0.15	<0.11	0.14	0.15	<0.11	--	<0.12	<0.13±0.02
Tape strip 11-15	--	--	--	--	<0.11	<0.11	--	--	<0.11±0.00
TOTAL Tape strips 3+ [a]	0.33	0.48	0.44	0.47	0.59	0.55	0.54	0.48	0.49±0.08
TOTAL DOSE SITE	**4.53**	**2.48**	**0.44**	**0.67**	**1.29**	**1.75**	**1.64**	**1.08**	**1.74±1.30**
Receptor fluid (0 - 12h)	<0.0006	<0.0007	0.0009	0.0021	0.0010	<0.0005	0.0017	0.0026	0.0013±0.0008
Receptor fluid (0 - 24h)	<0.0011	<0.0012	0.0022	0.0027	0.0016	0.014	0.0022	0.0031	0.0019±0.0007
%Ratio receptor 12h/24h	54	58	50	78	63	36	77	84	**68**
Receptor chamber wash	<0.000	<0.000	<0.000	<0.000	<0.000	<0.000	<0.000	0.003	<0.001±0.001
TOTAL DIRECT	**0.0017**	**0.0019**	**0.0031**	**0.0048**	**0.0026**	**0.0145**	**0.0039**	**0.0087**	**0.0052±0.0044**
POTENTIAL (dose site+ receptor)	**4.5317**	**2.4819**	**0.4431**	**0.6748**	**1.2926**	**1.7645**	**1.6439**	**1.0887**	**1.7402±1.2981**
POTENTIAL (skin+ receptor)	4.2017	2.0019	0.1031	0.2048	0.7026	1.2145	1.1039	0.6087	1.2677±1.3318
TOTAL RECOVERY	**87.49**	**104.12**	**103.49**	**111.38**	**102.04**	**109.90**	**131.32**	**105.85**	**106.95±12.23**

Evaluation according to EFSA Guidance	
Absorption >75% within half of study duration?	No. (include tape strip values except 1 &2)
Recovery <95%?	No
Total % Potentially Absorbable adjusted according to EFSA (2017)	1.7402±1.2981 1.7402 + 1.09 (k=0.84) **2.8%**

[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.

Distribution of radioactivity at 24 hours after dose application of ^{65}Copper hydroxide in a WG 53.8 formulation (Dilution II) to human skin samples (All cells).

	Distribution of radioactivity (% dose applied)								N= 8 K N° = 0.84
Donor N°	**1**	**1**	**2**	**2**	**3**	**3**	**4**	**4**	
Sex	F	F	F	F	F	F	F	F	
Cell N°	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	MEAN±SD
Skin wash 6h	93.1	77.0	91.0	98.3	97.0	88.5	90.0	86.4	90.1±6.7
Skin wash 24h	9.8	10.0	5.7	5.1	7.7	6.6	7.3	7.7	7.49±1.76
Tape strip 1	<1.07	<1.07	<1.07	<1.07	<1.07	<1.09	<1.36	<1.37	<1.15±0.13
Tape strip 2	<1.07	<1.07	<1.07	<1.07	<1.07	<1.09	<1.36	<1.37	<1.15±0.13
Total tape strips 1 + 2	2.14	2.14	2.14	2.14	2.14	2.18	2.72	2.74	2.29±0.27
Donor chamber	0.30	0.34	0.28	0.21	0.36	0.22	0.63	0.56	0.36±0.15
TOTAL NON-ABSORBED	**105.34**	**89.48**	**99.12**	**105.72**	**107.2**	**97.5**	**100.65**	**97.4**	**100.31±5.83**
Stripped skin	2.4	1.5	<1.0	<1.0	<1.0	<1.1	2.8	3.8	1.83±1.06
Tape strip 3	<1.07	<1.07	<1.07	<1.07	1.23	<1.09	<1.36	<1.37	<1.17±0.13
Tape strip 4	<1.07	<1.07	<1.07	<1.07	<1.07	<1.09	<1.36	<1.37	<1.15±0.13
Tape strip 5	<1.07	<1.07	<1.07	<1.07	<1.07	<1.09	<1.36	<1.37	<1.15±0.13
Tape strip 6-10	<1.07	<1.07	<1.07	<1.07	<1.07	<1.09	<1.36	<1.37	<1.15±0.13
Tape strip 11-15	<1.07	<1.07	<1.07	<1.07	<1.07	<1.09	--	<1.37	<1.12±0.11
TOTAL Tape strips 3+ [a]	5.35	5.35	5.35	5.35	5.51	5.45	5.44	6.85	5.58±0.52
TOTAL DOSE SITE	**7.75**	**6.85**	**6.35**	**6.35**	**6.51**	**6.55**	**8.24**	**10.65**	**7.41±1.48**
Receptor fluid µg (0 - 12h)	0.0008	0.0010	0.0007	0.0008	0.0010	0.0007	0.0011	<0.0006	0.0008±0.0002
Receptor fluid µg (0 - 24h)	0.0018	0.0016	<0.0013	<0.0014	<0.0016	<0.0013	<0.0017	<0.0011	<0.0015±0.0002
%Ratio receptor 12h/24h	44	63	54	57	63	54	65	55	**53**
Receptor fluid (%)	0.07	0.06	<0.05	<0.05	<0.06	<0.05	<0.08	<0.06	<0.06±0.01
Receptor chamber wash	<0.004	<0.004	0.008	<0.003	<0.004	0.013	<0.003	<0.003	<0.005±0.003
TOTAL DIRECT	**0.074**	**0.064**	**0.058**	**0.053**	**0.064**	**0.063**	**0.083**	**0.063**	**0.0653±0.0093**
POTENTIAL (dose site+ receptor)	**7.824**	**6.914**	**6.408**	**6.403**	**6.574**	**6.613**	**8.323**	**10.713**	**7.4715±1.4872**
POTENTIAL (skin+ receptor)	2.474	1.564	1.058	1.053	1.064	1.163	2.883	3.863	1.9±1.1.064
TOTAL RECOVERY	**113.16**	**96.39**	**105.53**	**112.12**	**113.77**	**104.11**	**108.97**	**108.11**	**107.8±5.8**

Evaluation according to EFSA Guidance	
Absorption >75% within half of study duration?	No. (include tape strip values except 1 &2)
Recovery <95%?	No
Total % Potentially Absorbable adjusted according to EFSA (2017)	**7.4715±1.4872 = 7.5%**

[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.

Conclusion:

The dermal penetration through human dermatomed skin of ^{65}Copper hydroxide in a WG 53.8 formulation was investigated at three nominal concentrations corresponding to the neat product (350 g /kg) and to two representative spray dilutions of 3 g/L and 0.3 g/L.

Concentrate

The mean percentage of ^{65}Copper hydroxide in the WG 53.8 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 0.39%.

Intermediate Dose level (Spray dilution at 3 g/L)

The mean percentage of ^{65}Copper hydroxide in the WG 53.8 formulation that was considered to be potentially absorbable for the spray dilution at 3 g/L applying the EFSA guidance (2017) to the study data was 2.8%.

Low Dose level (Spray dilution at 0.3 g/L)

The mean percentage of ^{65}Copper hydroxide in the WG 53.8 formulation that was considered to be potentially absorbable for the spray dilution at 0.3 g/L applying the EFSA guidance (2017) to the study data was 7.5%.

Therefore, the following dermal absorption values can be proposed for Copper hydroxide in the WG 53.8 formulation:

- 0.39% for the neat formulation (350 g/kg)
- 2.8% for the intermediate dose (3 g/L)
- 7.5% for the low dose (0.3 g/L)

Although the above values have been determined in accordance with the EFSA guidance on dermal absorption (2017), it is noted that this is overly conservative in the case of copper, as the amount retained in the stratum corneum and stripped skin is not likely to be available for systemic absorption over time.

Reference	**KCP 7.3/02**
Report	*In vitro* percutaneous absorption of copper, formulated as Copper Hydroxide (DPX-GFJ52) 53.8WG (35% as metallic copper), through rat skin xxx (2016) Du-Pont-42649
Guideline(s)	OECD 428 (2004); OECD Assessment No 28, (2004); EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption (2017)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	Not relevant

Material and methods:

Rat skin:	Source: Wistar WU, Harlan Number and sex: 3 male rats, 10-12 weeks old. Anatomical region: Dorsal. Thickness: Dermatomed to 200 to 400 µm.
Test Material:	
Non-radiolabeled:	Copper hydroxide
Radiolabeled:	^{65}Copper hydroxide
Formulation:	The formulation used in this experiment was Copper hydroxide 53.8 WG containing nominal 53.8% ^{65}Copper hydroxide (equivalent to 35% metallic copper). It was used at three nominal concentrations of copper hydroxide: neat (317 ± 17 g/kg) with 2 spray dilutions of 3 g ^{65}Copper. L^{-1} and 0.3 g ^{65}Copper. L^{-1}.

Test system:

A flow-through diffusion cell system (Perm Gear Inc., Riegelsville, PA, USA) was used to study the absorption of the test substance. Approximately 20 h prior to exposure, the split-thickness skin membranes were placed in the 9 mm flow through automated diffusion cells to hydrate the skin. The skin surface temperature was set at 32 ± 1˚C and the humidity was ambient. Following application of the test preparations, the actual temperature was recorded at 15-minute intervals during the study in a diffusion cell containing a non-exposed skin membrane. The receptor fluid was pumped at a speed of approximately 1.2 $mL.h^{-1}$ and consisted of Phosphate buffered saline (PBS) containing 0.01% sodium azide (w/v), supplemented with 6% polyoxy-ethylene 20-oleyl glycol (PEG) (w/v), pH 7.2.
In the flow through cells used the volume of receptor fluid in the receptor chamber beneath the skin was approximately 0.2 mL. At a flow rate of 1.2 $mL.h^{-1}$, this volume was replenished continuously (6 times/hour) such that the rate of diffusion into the receptor fluid did not become a rate limiting step.

Skin integrity:

After placing the skin membranes in the diffusion cells, membrane integrity was assessed. 200 µL saline (containing 0.01% sodium azide) and titrated water was applied in the donor compartment of the flow through diffusion cells. The compartment was covered with a glass slide. Samples of the receptor fluid (approx. 1.8 mL/hour) were collected every hour up to three hours following application and measured for radioactivity using liquid scintillation counting (LSC). Titrated water remaining at the application site was removed and the skin dried with cotton swabs. Membranes were stored overnight to allow washout.
Membranes with a permeability coefficient (K_p) for water less than 2.5×10^{-3} $cm.h^{-1}$ were taken forward for use in the study.
Skin membranes used for replicates B-5 and C-7 were erroneously included when they should have been excluding following integrity tests. They were excluded from the calculations.

Treatment:

The undiluted concentrate (powder) was distributed over the skin and wetted using a minimal volume of artificial sweat (to mimic conditions on the skin under occlusive clothing conditions).
For the dilutions, the dose preparations were applied to the split-thickness skin sample with a pipette at the rate of approximately 10 $\mu L/cm^2$ exposed skin.
The exposure period was 6-hours for all skin preparations.

Sampling:

24-hours following application, the mass balance was determined, which comprised measurements from the receptor fluid, skin wash, receptor compartment wash, donor compartment wash, pooled tape strips and stripped skin.
Receptor fluid samples were collected at 0-1, 1-2, 2-4, 4-6, 6-12- and 12-24-hours following application. Following 6-hours' exposure, the unabsorbed test substance was removed with mild soap and cotton swabs and dried. A second skin wash was similarly performed at 24-hours post-application and

	the diffusion cell was dismantled (receptor and donor compartments were washed with ethanol and water). Each skin membrane was tape stripped 15 times (unless epidermis rupture occurred). Tape strips were pooled as 1, 2, 3, 4, 5, 6-10 and 11-15. Following tape stripping the membranes were collected and stored until analysis.
Radioassay:	The amounts of radioactivity in the membrane integrity test samples were determined by liquid scintillation counting (LSC). The amount of copper was determined at mass 65 m/z and mass 63 m/z using a double focusing high resolution inductively coupled plasma spectrometry (HR-ICP-MS) in medium mode (resolution, 40000) in all collected samples.

Results:

Copper was demonstrated to be sufficiently soluble in the receptor fluid to avoid any risk of back diffusion.

Measurements of the homogeneity of the three concentrations of formulation applied indicated that it was acceptable.

The study results are presented in the following Tables:

Distribution of radioactivity at 24 hours after dose application of ^{65}Copper hydroxide in a WG 53.8 formulation (undiluted concentrate) to rat skin samples (All cells).

	Distribution of radioactivity (% dose applied)								N= 7 K N° = 0.92
Donor N°	**1**	**1**	**2**	**2**	**3***	**3**	**1**	**2**	
Sex	M	M	M	M	M	M	M	M	
Cell N°	A-1	A-2	A-3	A-4	A-5	A-6	A-7	A-8	MEAN±SD
Skin wash 6h	118.2	108.3	116.1	101.7	99.2	98.5	108.6	97.8	107.0±8.1
Skin wash 24h	1.5	1.2	1.7	1.9	1.1	0.9	1.0	0.9	1.3±0.4
Tape strip 1	0.20	0.13	0.16	0.16	0.08	0.14	0.13	0.17	0.16±0.03
Tape strip 2	0.10	0.10	0.06	0.07	0.06	0.05	0.06	0.10	0.08±0.02
Total tape strips 1 + 2	0.3	0.23	0.22	0.23	0.14	0.19	0.19	0.27	0.23±0.04
Donor chamber	0.01	0.00	0.00	0.03	0.03	0.01	0.00	0.00	0.008±0.010
TOTAL NON-ABSORBED	**120.01**	**109.73**	**118.02**	**103.86**	**100.47**	**99.6**	**109.79**	**98.97**	**108.57±8.34**
Stripped skin	1.42	0.38	2.47	1.43	1.61	0.57	1.73	1.26	1.32±0.70
Tape strip 3	0.04	0.13	0.10	0.22	0.02	0.04	0.29	0.29	0.16±0.11
Tape strip 4	0.09	0.20	0.08	0.08	0.01	0.06	--	--	0.10±0.05
Tape strip 5	0.12	0.16	0.07	0.06	0.01	0.06	--	--	0.09±0.05
Tape strip 6-10	--	0.15	0.23	0.12	0.05	0.07	--	--	0.14±0.07
Tape strip 11-15	--	--	0.33	0.15	0.02	0.05	--	--	0.18±0.14
TOTAL Tape strips 3+ [a]	0.25	0.64	0.81	0.63	0.11	0.28	0.29	0.29	0.46±0.23
TOTAL DOSE SITE	**1.67**	**1.02**	**3.28**	**2.06**	**1.72**	**0.85**	**2.02**	**1.55**	**1.78±0.81**
Receptor fluid µg (0 - 12h)	0.004	0.020	0.115	0.129	15.826	0.057	1.356	0.032	0.24±0.49
Receptor fluid µg (0 - 24h)	0.008	0.068	0.399	0.133	15.829	0.077	2.163	0.034	0.41±0.78
%Ratio receptor 12h/24h	50	29	29	97	97	74	63	94	**56**
Receptor fluid (%)	0.001	0.004	0.027	0.008	1.161	0.005	0.131	0.002	0.025±0.047
Receptor chamber wash	0.00	0.00	0.001	0.001	0.309	0.003	0.00	0.00	0.001±0.001
TOTAL DIRECT	**0.001**	**0.004**	**0.028**	**0.009**	**1.47**	**0.008**	**0.131**	**0.002**	**0.0261±0.0471**
POTENTIAL (dose site+ receptor)	**1.671**	**1.024**	**3.308**	**2.069**	**3.19**	**0.858**	**2.151**	**1.552**	**1.8047±0.8203**
POTENTIAL (skin+ receptor)	1.421	0.384	2.498	1.439	3.08	0.578	1.861	1.262	1.3490±0.7221
TOTAL RECOVERY	**121.68**	**110.75**	**121.33**	**105.93**	**103.66**	**100.46**	**111.94**	**100.52**	**110.37±8.81**

Evaluation according to EFSA Guidance	
Absorption >75% within half of study duration?	No. (include tape strip values except 1 &2)
Recovery <95%?	No
Total % Potentially Absorbable adjusted according to EFSA (2017)	**1.8±0.82 = 1.8 + 0.75 (K=0.92) 2.6%**
[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.	

*replicate A-5 was excluded from the calculations owing to a deviating absorption profile caused by damaged membrane integrity.

Distribution of radioactivity at 24 hours after dose application of ^{65}Copper hydroxide in a WG 53.8 formulation (Dilution I) to rat skin samples (All cells).

	Distribution of radioactivity (% dose applied)								N= 6 K N° = 1
Donor N°	**1**	**1**	**2**	**2**	**3***	**3**	**3***	**1**	
Sex	M	M	M	M	M	M	M	M	
Cell N°	B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	MEAN±SD
Skin wash 6h	97.8	91.5	78.3	81.8	67.4	84.9	78.0	103.7	89.7±9.8
Skin wash 24h	6.1	9.5	10.7	9.6	4.6	8.4	10.9	11.4	9.3±1.9
Tape strip 1	1.18	4.66	3.74	5.32	2.73	2.33	5.24	4.14	3.56±1.54
Tape strip 2	0.74	2.09	3.63	2.62	1.24	2.19	2.90	2.94	2.37±0.97
Total tape strips 1 + 2	1.92	6.75	7.37	7.94		4.52		1.08	5.93±2.29
Donor chamber	0.04	0.05	0.04	0.04	0.05	0.05	0.06	0.08	0.05±0.01
TOTAL NON-ABSORBED	**105.86**	**107.8**	**96.41**	**99.38**		**97.87**		**116.26**	**103.93±7.55**
Stripped skin	1.6	0.5	2.6	2.9	2.4	1.2	2.7	1.5	1.7±0.9
Tape strip 3	0.46	1.40	1.46	1.39	0.97	1.50	2.54	2.06	1.38±0.52
Tape strip 4	0.67	1.51	1.36	0.52	1.17	1.55	0.93	1.20	1.14±0.44
Tape strip 5	0.31	0.92	4.02	0.64	0.46	0.93	0.83	0.78	1.27±1.37
Tape strip 6-10	--	1.21	3.31	0.58	2.37	1.64	--	0.70	1.49±1.10
Tape strip 11-15	--	--	--	--	0.79	0.47	--	--	0.47
TOTAL Tape strips 3+ [a]	1.44	5.04	10.15	3.13		6.09		4.74	5.10±2.96
TOTAL DOSE SITE	**3.04**	**5.54**	**12.75**	**6.03**		**7.29**		**6.24**	**6.82±3.23**
Receptor fluid µg (0 - 12h)	0.01	0.07	0.28	0.20	5.97	0.15	1.75	0.04	0.12±0.10
Receptor fluid µg (0 - 24h)	0.01	0.09	0.41	0.20	5.97	0.16	2.22	0.04	0.15±0.14
%Ratio receptor 12h/24h	100	77	68	100	100	94	79	100	**80**
Receptor fluid (%)	0.039	0.365	1.593	0.775	23.126	0.613	8.597	0.174	0.59±0.56
Receptor chamber wash	0.001	<0.001	0.006	0.036	0.303	0.002	0.007	0.008	0.009±0.014
TOTAL DIRECT	**0.04**	**0.366**	**1.599**	**0.811**		**0.615**		**0.182**	**0.6022±0.5632**
POTENTIAL (dose site+ receptor)	**3.08**	**5.906**	**14.349**	**6.841**		**7.905**		**6.422**	**7.4172±3.7605**
POTENTIAL (skin+ receptor)	1.64	0.866	4.199	3.711		1.815		1.682	2.3188±1.3194
TOTAL RECOVERY	**108.94**	**113.71**	**110.76**	**106.22**		**105.78**		**122.68**	**111.35±6.29**

Evaluation according to EFSA Guidance	
Absorption >75% within half of study duration?	Yes (exclude all tape strips)
Recovery <95%?	No
Total % Potentially Absorbable adjusted according to EFSA (2017)	**2.3188±1.3194 (k=1) 3.6%**

[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.

*replicates B-5 and B-7 were excluded from the calculations owing to a deviating absorption profile caused by damaged membrane integrity.

Distribution of radioactivity at 24 hours after dose application of ^{65}Copper hydroxide in a WG 53.8 formulation (Dilution II) to rat skin samples (All cells).

	Distribution of radioactivity (% dose applied)								N= 6 K N° = 1
Donor N°	**1**	**1**	**2**	**2**	**3***	**3**	**2***	**3**	
Sex	M	M	M	M	M	M	M	M	
Cell N°	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	MEAN±SD
Skin wash 6h	91.0	84.5	73.4	86.4	85.1	78.0	88.2	35.8	74.9±20.1
Skin wash 24h	12.5	10.1	10.0	8.1	7.8	9.0	6.6	11.7	10.24±1.67
Tape strip 1	<0.90	0.91	<0.90	<0.90	<0.90	<0.89	2.97	1.61	<1.02±0.29
Tape strip 2	<0.90	<0.90	<0.90	<0.90	<0.90	<0.89	<0.90	<0.91	<0.90±0.00
Total tape strips 1 + 2	1.8	1.81	1.8	1.8		1.78		2.52	1.92±0.29
Donor chamber	0.91	0.93	0.85	0.91	0.90	0.86	0.23	0.98	0.91±0.05
TOTAL NON-ABSORBED	**106.21**	**97.34**	**86.05**	**97.21**		**89.64**		**51**	**87.91±19.39**
Stripped skin	2.1	3.2	4.5	3.5	5.6	5.2	11.9	8.6	4.50±2.27
Tape strip 3	<0.90	<0.90	<0.90	<0.90	<0.90	<0.89	<0.90	<0.91	<0.90±0.00
Tape strip 4	<0.90	<0.90	<0.90	<0.90	<0.90	<0.89	<0.90	<0.91	<0.90±0.01
Tape strip 5	<0.90	<0.90	<0.90	<0.90	<0.90	<0.89	<0.90	<0.91	<0.90±0.00
Tape strip 6-10	3.97	2.03	4.17	3.73	2.20	1.75	2.58	2.33	3±1.08
Tape strip 11-15	<0.90	3.11	0.95	1.87	2.52	2.28	-	2.43	1.93±0.87
TOTAL Tape strips 3+ [a]	7.57	7.84	7.82	8.3		6.7		7.49	7.62±0.53
TOTAL DOSE SITE	**9.67**	**11.04**	**12.32**	**11.8**		**11.9**		**16.09**	**12.14±2.15**
Receptor fluid µg (0 - 12h)	0.007	0.058	0.291	0.171	2.504	0.116	0.736	0.040	0.114±0.105
Receptor fluid µg (0 - 24h)	0.009	0.065	0.326	0.173	2.507	0.120	0.885	0.042	0.123±0.115
%Ratio receptor 12h/24h	78	89	89	99	100	97	83	95	**93**
Receptor fluid Total	0.36	2.58	12.82	6.85	99.26	4.68	34.73	1.69	**4.83±4.54**
Receptor chamber wash	<0.009	0.016	0.019	<0.008	<0.008	0.017	0.075	0.016	0.014±0.004
TOTAL DIRECT	**0.369**	**2.596**	**12.839**	**6.858**		**4.697**		**1.706**	**4.8442±4.5370**
POTENTIAL (dose site+ receptor)	10.039	13.636	25.159	18.658		16.597		17.796	16.9808±5.0967
POTENTIAL (skin+ receptor)	**2.469**	**5.796**	**17.339**	**10.358**		**9.897**		**10.306**	**9.3608±5.0206**
TOTAL RECOVERY	**116.25**	**110.98**	**111.21**	**115.87**		**106.24**		**68.80**	**104.89±18.06**

Evaluation according to EFSA Guidance	
Absorption >75% within half of study duration?	Yes (Exclude all tape strips)
Recovery <95%?	No
Total % Potentially Absorbable adjusted according to EFSA (2017)	**9.3608±5.0206 (k=1) 14%**

[a]: tape-strips excluding numbers 1 & 2 which are considered to be non-absorbed dose.

*replicates C-5 and C-7 were excluded from the calculations owing to a deviating absorption profile caused by damaged membrane integrity.

Conclusion:

The dermal penetration through rat dermatomed skin of ^{65}Copper hydroxide in a WG 53.8 formulation was investigated at three nominal concentrations corresponding to the neat product (350 g /kg) and to two representative spray dilutions of 3 g/L and 0.3 g/L.

Concentrate

The mean percentage of ^{65}Copper hydroxide in the WG 53.8 formulation that was considered to be potentially absorbable for the neat formulation applying the EFSA guidance (2017) to the study data was 2.6%.

Intermediate Dose level (Spray dilution at 3 g/L)

The mean percentage of ^{65}Copper hydroxide in the WG 53.8 formulation that was considered to be potentially absorbable for the spray dilution at 3 g/L applying the EFSA guidance (2017) to the study data was 3.6%.

Low Dose level (Spray dilution at 0.3 g/L)

The mean percentage of ^{65}Copper hydroxide in the WG 53.8 formulation that was considered to be potentially absorbable for the spray dilution at 0.3 g/L applying the EFSA guidance (2017) to the study data was 14%.

Therefore, the following dermal absorption values can be proposed for Copper hydroxide in the WG 53.8 formulation:

- 2.6% for the neat formulation (350 g/kg)
- 3.6% for the intermediate dose (3 g/L)
- 14% for the low dose (0.3 g/L)

Although the above values have been determined in accordance with the EFSA guidance on dermal absorption (2017), it is noted that this is overly conservative in the case of copper, as the amount retained in the stratum corneum and stripped skin is not likely to be available for systemic absorption over time and in actual fact, these compartments should be excluded from the calculations.

Reference	**KCP 7.3/03**
Report	*In vivo* percutaneous absorption of copper, formulated as Copper Hydroxide (DPX-GFJ52) 53.8WG (35% as metallic copper), in rats xxx (2016) xxx-42648
Guideline(s)	OECD 427 (2004); OECD Assessment No 28, (2004); EFSA Panel on Plant Protection Products and their Residues (PPR): Guidance on Dermal Absorption (2017)
Deviations	No
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	Not relevant

Materials and methods:

Test animals:	
Species:	Rat
Strain:	Wistar (HsdCpb:Wu)
Number, sex	36 males
Age:	9-10 weeks
Weight at dosing:	296-332g (group A; concentrate), 295-330g (group B; dilution I), 286-333g (group C; dilution II)
Source:	xxxx, The Netherlands
Acclimation period:	At least 5 days (including 1 day in metabolism cages)
Identification:	Tail markings and cage cards

Diet:	Commercial rodent diet (SDS, Witham, England)
Water:	Provided *ad libitum*
Housing:	Nalgene metabolic cages
Temperature:	22±2˚C
Humidity:	45-65%
Photoperiod:	12 hours light/12 hours dark
Air changes	9-11 changes/hour

Test Material:

Non-radiolabelled: Copper hydroxide

Radiolabelled: ^{65}Copper hydroxide

Formulation: The formulation used in this experiment was Copper hydroxide 53.8 WG containing nominal 53.8% ^{65}Copper hydroxide (equivalent to 35% metallic copper).
It was used at three nominal concentrations of copper hydroxide: neat (317 ± 17 g/kg) with 2 spray dilutions of 3 g ^{65}Copper. L^{-1} and 0.3 g ^{65}Copper. L^{-1}.

Test system: The dermal absorption of ^{65}Copper hydroxide was investigated in 3 groups of male rats, each comprising 3 subgroups of 4 animals as follows:

- Group A, undiluted concentrate, comprising time groups AT1 (24h), AT2 (72h) & AT3 (144h)
- Group B, spray dilution I, comprising time groups BT1 (24h), BT2 (72h) & BT3 (144h)
- Group C, spray dilution II, comprising time groups CT1 (24h), CT2 (72h) & CT3 (144h)

The extended time periods after the test material was washed off the skin at 6 hours, provided additional information on the bioavailability of the test substance after passing the epidermis and entering the systemic circulation.

Treatment: At least 24-hours prior to dosing, each animal had an area of 20 cm^2 clipped between the dorsal and shoulder region (care was taken to avoid skin damage). The area was swabbed with acetone and checked for abrasions; only rats with intact skin were used. Following shaving and skin wash the animals were moved to metabolism cages.

In all groups, the test substance was applied *via* dermal application on a dorsal area of approximately 10 cm^2 limited by an 'O' ring under semi-occlusive conditions (plastic cover and permeable tape) using the following methods:

- Group A: the skin was moistened with physiological saline and an appropriate amount of weighed test substance was applied to the skin and evenly spread within the 'O' ring.
- Groups B & C: the formulations were vortexed and checked for homogeneity. 100 µL of test substance was applied to the area with a pipette and evenly spread within the 'O' ring.

The exposure period was 6-hours for all animals and the rats were subsequently maintained until 24, 72 and 144 hours post-dose (18, 66 & 138 hours post exposure).

Sampling:

Skin washing: 6 hours following initiation of exposure, the 'O' ring was removed and retained, and the skin washed 9 times with mild soap solution.

Excreta: Urine and faeces were collected at 24-hour intervals until sacrifice. After each 24-hour collection the cages were washed, and faeces was mixed with 3 parts water and weighed and homogenised ready for analysis.

Sacrifice: Animals were sacrificed by exsanguination following anaesthesia. At sacrifice the following samples were collected; 'O' ring and protective device, skin wash at sacrifice, individual surface tape strips (*stratum corneum*) to a maximum of 15, post-stripping application site, non-treated skin, whole blood, plasma, GI-tract, and residual carcass.

Controls:

Urine, faeces, and tissues were collected from untreated control animals. In addition, blank materials and cage wash solutions were collected.

Radioassay:

The amount of copper was determined at mass 65 m/z and mass 63 m/z using a double focusing high resolution inductively coupled plasma spectrometry (HR-ICP-MS) in medium mode (resolution, 40000) in all collected samples.

Pilot study:

Due to the fact that copper is abundantly available from various sources, a pilot study was undertaken to determine the background levels of copper in various matrices and samples of untreated rats and to ascertain the feasibility of analysing copper in the various matrices.

Results and discussion:

Measurements of the homogeneity of the three concentrations of formulation applied indicated that it was acceptable. The actual administered doses for the concentrate were slightly higher than intended, recoveries for this group ranged from 94.6% to 96.5%.

There were no deaths or clinical signs of toxicity in the animals. Body weights at sacrifice were only slightly lower compared with the start of treatment with no dose response and were considered to be secondary to housing and devices used in the study and not a treatment related effect.

Absorption and excretion

For the undiluted concentrate, after 24-hours, <0.051% of the applied dose was absorbed and the recovery was comparable after 72 hours (<0.042%) and 144 hours (<0.047%), indicating the amount present in the stratum corneum and stripped skin was not systemically available. This is supported by the fact that the amount present in the stratum corneum or stripped skin did not decrease over time.

It was not possible to determine the levels of Cu for the 2 spray dilutions because of high amounts of endogenous copper in the urine, faeces, cage wash, blood, GI tract and carcass; therefore, absorption was only determined in the unabsorbed fractions as well as control skin, stripped skin and tape strips. Based on the very low absorption found for the concentrate formulation and considering the good recoveries for the field dilutions, it is concluded that only a negligible amount of applied copper was absorbed from either dilution.

Tape stripping

Tape stripping in all groups revealed that most of the applied ^{65}Cu was concentrated in the upper layers of the stratum corneum at 144 hours post application.

In the undiluted concentrate group, the amount of ^{65}Cu in tape strips 3+ after 24 hours was 0.056% of the administered dose and decreased only very slightly to 0.022% at 144 hours following dosing, confirming that little to no absorption from the application site occurs, resulting in very low systemic uptake (below the LoD).
In the spray dilution groups, the amount in tape strips 3+ after 24 hours was 0.61% and 2.50% for dilutions I and II, respectively. Again, decreasing only slightly to 0.46% and 1.90% respectively after 144 hours. The total amount in all tape strips (1+) was constant across the time groups, indicating that little to no ^{65}Cu becomes systemically available over time.
Stripped skin
After 24 hours the amount in the stripped skin was 0.009% of the administered concentrate, after 72 and 144 hours, 0.002% and <0.001% was found. For spray dilution I the majority of stripped skin (except one animal) was below the LoD resulting in <0.04% and <0.02% of the administered dose being recovered at 24 and 144 hours. Similarly, for dilution II all of the stripped skin except one animal was below the LoD, resulting in <0.29% and 0.17% of the administered dose being recovered at 24 and 144 hours. This indicates that little to no ^{65}Cu form the stripped skin compartment becomes systemically available over time.
Carcass and blood
For the concentrate, 0.019%, 0.014% and <0.005% were found in the residual blood at 24, 72 and 144 hours. It was not possible to determine the levels of ^{65}Cu in the blood or residual carcass because of the high background levels of endogenous copper present in these matrices.
The results are presented in the tables below:

Distribution of radioactivity at 24, 72 and 144 hours after dose application of ^{65}Copper hydroxide in a WG 53.8 formulation (undiluted concentrate) to rats.

	AT1 (24h)		**AT2 (72h)**		**AT3 (144h)**	
	Mean	SD	Mean	SD	Mean	SD
Urine (total)	<0.001	-	<0.001	-	<0.002	-
Faeces (total)	<0.001	-	<0.018	-	<0.035	-
Cage wash	<0.001	-	<0.003	-	<0.002	-
Blood	<0.001	-	<0.001	-	<0.001	-
Control skin	<0.001	-	<0.001	-	<0.001	-
GI tract	<0.002	-	<0.002	-	<0.002	-
Carcass	<0.025	-	<0.017	-	<0.007	-
Stripped skin	0.009	0.012	0.002	0.002	<0.001	<0.001
Absorbed	**<0.051**	**0.044**	**<0.042**	**0.027**	<0.047	**0.005**
Total skin wash[1]	94.31	0.86	96.32	1.70	94.71	1.66
O-ring/cover	0.17	0.12	0.11	0.08	0.12	0.08
Tape strips (3+)[2]	0.06	0.04	0.03	0.04	0.02	0.01
Not absorbed	**94.54**	**0.95**	**96.46**	**1.63**	**94.85**	**1.57**
Recovery	**94.59**	**0.94**	**96.50**	**1.61**	**94.90**	**1.57**

[1]including tape strips 1 & 2 (values below the LoD were considered as the LoD for the calculations
[2]tape strip 3 to the final tape strip taken (up to 15)

Distribution of radioactivity at 24, 72 and 144 hours after dose application of ^{65}Copper hydroxide in a WG 53.8 formulation (Dilution I) to rats.

	BT1 (24h)		BT2 (72h)		BT3 (144h)	
	Mean	SD	Mean	SD	Mean	SD
Urine (total)	n.m.	-	n.m.	-	n.m.	-
Faeces (total)	n.m.	-	n.m.	-	n.m.	-
Cage wash	n.m.	-	n.m.	-	n.m.	-
Blood	n.m.	-	n.m.	-	n.m.	-
Control skin	0.01	-	0.01	-	0.01	-
GI tract	n.m.	-	n.m.	-	n.m.	-
Carcass	n.m.	-	n.m.	-	n.m.	-
Stripped skin	<0.04	-	<0.02	-	<0.02	-
Absorbed	**n.a**	-	**n.a**	-	**n.a**	-
Total skin wash[1]	95.24	3.19	100.41	2.56	99.17	1.30
O-ring/cover	0.18	0.05	0.12	0.05	0.22	0.06
Tape strips (3+)[2]	0.61	0.22	0.45	0.39	0.46	0.21
Not absorbed	**96.04**	**3.16**	**100.98**	**2.26**	**99.85**	**1.47**
Recovery	**96.08**	**3.15**	**101.00**	**2.26**	**99.88**	**1.47**

[1]including tape strips 1 & 2 (values below the LoD were considered as the LoD for the calculations
[2]tape strip 3 to the final tape strip taken (up to 15)
n.m = not measured, n.a = not applicable

Distribution of radioactivity at 24, 72 and 144 hours after dose application of ^{65}Copper hydroxide in a WG 53.8 formulation (Dilution II) to rats.

	CT1 (24h)		CT2 (72h)		CT3 (144h)	
	Mean	SD	Mean	SD	Mean	SD
Urine (total)	n.m.	-	n.m.	-	n.m.	-
Faeces (total)	n.m.	-	n.m.	-	n.m.	-
Cage wash	n.m.	-	n.m.	-	n.m.	-
Blood	n.m.	-	n.m.	-	n.m.	-
Control skin	<0.10	-	<0.10	-	<0.10	-
GI tract	n.m.	-	n.m.	-	n.m.	-
Carcass	n.m.	-	n.m.	-	n.m.	-
Stripped skin	<0.29	-	<0.17	-	<0.17	-
Absorbed	**n.a**	-	**n.a**	-	**n.a**	-
Total skin wash[1]	94.75	94.89	95.80	1.56	94.78	1.29
O-ring/cover	0.65	0.77	1.20	0.28	0.95	0.30
Tape strips (3+)[2]	2.50	1.11	1.37	0.18	1.90	0.59
Not absorbed	**97.41**	**0.85**	**98.38**	**1.37**	**97.63**	**1.23**
Recovery	**97.80**	**0.76**	**98.64**	**1.38**	**97.89**	**1.23**

[1]including tape strips 1 & 2 (values below the LoD were considered as the LoD for the calculations
[2]tape strip 3 to the final tape strip taken (up to 15)
n.m = not measured, n.a = not applicable

The *in vivo* dermal penetration in rats of ^{65}Copper hydroxide in a WG 53.8 formulation was investigated at three nominal concentrations corresponding to the neat product (350 g /kg) and to two representative spray dilutions of 3 g/L and 0.3 g/L.

Concentrate

After 24 hours, <0.051% of the applied dose was absorbed (sum of excreta, GI tract, Stripped skin, and carcass). The absorption was comparable after 72 and 144 hours (<0.042% and <0.047%).

Mean recovery within the time groups was 94.59% to 96.50%.

Intermediate Dose level (Spray dilution at 3 g/L)

It was not possible to determine an increase in ^{65}Cu in the spray dilutions owing to the high levels of background endogenous copper in the matrices. However, owing to the small absorption for the concentrate and good recovery for the spray dilutions it is concluded that only a negligible amount of copper would be absorbed.

Mean recovery across the time groups was 96.08% to 101.0%.

Low Dose level (Spray dilution at 0.3 g/L)

It was not possible to determine an increase in ^{65}Cu in the spray dilutions owing to the high levels of background endogenous copper in the matrices. However, owing to the small absorption for the concentrate and good recovery for the spray dilutions it is concluded that only a negligible amount of copper would be absorbed.

Mean recovery across the time groups was 97.80% to 98.64%.

Conclusion:
The absorption of ^{65}Cu from the undiluted concentrate was <0.05% over 144 hours. For both spray dilutions, a worst-case assumption for absorption was determined from the non-absorbed fractions (owing to the high background levels of endogenous copper preventing measurement in some matrices). Based on the low absorption for the concentrate and the good recoveries for both dilutions from the non-absorbed fractions, it is concluded that very little absorption of applied copper had occurred in both field dilutions.
The amount of the applied dose of ^{65}CU in the stripped skin was very low; the largest amount being observed in dilution II at 24 hours (0.3%). The amount present in the stratum corneum showed no clear decrease over time and the majority remained in the upper layers.
Therefore, for all 3 dose levels the amount of ^{65}Cu located in the stratum corneum was not available for absorption under the conditions of the study.

Triple pack calculations
All three studies are comparable with regard to test material, formulation, vehicle, exposure etc. and fulfils all of the criteria for similarity as outlined in the EFSA guidance on dermal absorption (2017).
For the *in vivo* study, it is possible to use a worst-case value of 1.9% (which represents the mean missing recovery), by assuming that all of this amount is in the absorbed fraction. Therefore, the triple pack calculations for the highest dilution (0.3%) would be based on the following values:

- In vivo rat: 1.9%
- In vitro rat: 14%
- In vitro human: 7.5%

The dermal absorption value for the highest dilution can therefore be calculated as follows:

In vivo human % absorption=*in vivo* rat % absorption/*in vitro* rat % absorption x *in vitro* % human absorption

In vivo human % absorption = 1.9%/14% x 7.5% = 0.8%

Therefore, a dermal absorption value of 0.8% can be determined from the triple pack approach.
It is acknowledged however, that this is also a conservative approach as the values for the in vitro studies are likely to be an overestimation, owing to the inclusion of the tape-strips and the stripped skin in the final values, when it is unlikely that this an absorbable dose.

Applicant's comment:

In accordance with xxx (2020) a dermal absorption value of 0.1 % was used for the concentrate and 1 % was used for the dilution (please refer to KCP 7.3/04).

Concerning the triple pack study summaries; we have noticed an error in the calculation for the human in vitro calculation (dilution II). In the submitted summary the value for dilution II is reported as 7.5%, this value should actually be 8.6% (7.41±1.48 = 7.41 + 1.2 (k=0.84) = 8.6%). The previous value was not adjusted correctly to account for the standard deviation (k=0.84).

When fed into the triple pack calculation for dilution II, this results in a dermal absorption value of 1.2%, rather than the previously proposed 1% (see below):

Dilution II (0.3%)
The values used in the triple pack calculation for dilution II are:
- *In vivo rat: 1.9% (based on mean missing recovery as a worst case)*
- *In vitro rat: 14%*
- *In vitro human: 8.6%*

The dermal absorption value for the highest dilution can therefore be calculated as follows:

In vivo human % absorption=in vivo rat % absorption/in vitro rat % absorption x in vitro % human absorption

In vivo human % absorption = 1.9%/14% x 8.6% = 1.2%

Therefore, a dermal absorption value of 1.2% can be determined from the triple pack approach.

For transparency we would like to make you aware of this change; however, we propose to stick to a dermal absorption value of 1% for the calculations, which is still a conservative value supporting the proposed value of 0.5% (based on the previous in vitro studies and position papers), and the value of 0.8% for dilution I in the triple pack summaries. As you are aware, the dermal absorption is not inversely proportionate to concentration for copper, and any differences are solely a result of differences in LOQ values and not a true reflection of the dilution of the formulation.

A 2.11 Other/Special Studies

None.

Appendix 3 Exposure calculations

A 3.1.1 Operator exposure: Application rate 1.0 kg a.s./ha - Dutch greenhouse model

OPERATOR EXPOSURE			DUTCH GREENHOUSE MODEL	
form	Nordox 75 WG		Application including mixing and loading	
a.s.	Copper			
Parameter		**Value**	**Unit**	**References, comments**
MANUAL SPRAYING in greenhouses				
AR	Application rate	1	kg a.s./ha	summary of intended uses
A	Area treated	1	ha/ day	Dutch model
Inhalation Exposure				without PPE
SV	Surrogate Exposure Value	1	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
Inhalation Exposure (without PPE)		**1**	mg a.s./ day	IE = SV x AR x A
Inhalation Exposure (with PPE)				with PPE
	PPE-factor	10		Non-powered mask filtertype 2 (most conservative): 10; more advanced RPE: see note** (Dutch model)
Inhalation Exposure (with PPE)		**0.1**	mg a.s./ day	IE(PPE) = (1/PPE factor) x IE
Dermal Exposure				without PPE
SV	Surrogate Exposure Value	200	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
Dermal Exposure		**200**	mg a.s./ day	DE = SV x AR x A
Dermal Exposure (with PPE)				with PPE
	PPE-factor	10		Gloves + coverall: 10 (Dutch model)
Dermal Exposure (with PPE)		**20**	mg a.s./ day	DE(PPE) = (1/PPE-factor) x DE
Internal exposure				
IA	Inhalation Absorption	100	%	
DA	Dermal Absorption	1	%	
	AOEL	5.6	mg a.s./ day	based on 70 kg bw
		Without PPE	**With PPE**	
	Internal exposure	[mg a.s. / day]	[mg a.s. / day]	
	Inhalation	1.0000	0.1000	IE(int) = IE x (IA/100)
	Dermal	2.0000	0.2000	DE(int) = DE x (DA/100)
	Total	**3.0000**	**0.3000**	**sum**
	% AOEL			
	Inhalation	18	2	%AOEL = 100 x IE(int) / AOEL
	Dermal	36	4	%AOEL = 100 x DE(int) / AOEL
	Total	**54**	**5**	**sum**

* NOTE: The above mentioned model is for spraying in greenhouses. For dusting of carnations the surrogate values should be changed: inhalation should be 20 mg/kg instead of 1, and dermal should be 300 mg/kg instead of 200.

** Note: Only for gasforming/gaseous preparations and soil fumigation preparations: powered full-face filtering devices with filtertype 2 (factor 20), powered full-face filtering devices with filtertype 3 (factor 40)

A 3.1.2 Operator exposure: Application rate 1.0 kg a.s./ha - Dutch greenhouse model

OPERATOR EXPOSURE			DUTCH GREENHOUSE MODEL	
form	Nordox 75		Application including mixing and loading	
a.s.	Copper			
Parameter		**Value**	**Unit**	**References, comments**
MANUAL SPRAYING in greenhouses				
AR	Application rate	1	kg a.s./ha	summary of intended uses
A	Area treated	1	ha/ day	Dutch model
Inhalation Exposure				without PPE
SV	Surrogate Exposure Value	1	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
Inhalation Exposure (without PPE)		**1**	mg a.s./ day	IE = SV x AR x A
Inhalation Exposure (with PPE)				with PPE
	PPE-factor	1		Non-powered mask filtertype 2 (most conservative): 10; more advanced RPE: see note** (Dutch model)
Inhalation Exposure (with PPE)		**1**	mg a.s./ day	IE(PPE) = (1/PPE factor) x IE
Dermal Exposure				without PPE
SV	Surrogate Exposure Value	200	mg a.s./ kg a.s.	For dusting see note* (Dutch model)
Dermal Exposure		**200**	mg a.s./ day	DE = SV x AR x A
Dermal Exposure (with PPE)				with PPE
	PPE-factor	10		Gloves + coverall: 10 (Dutch model)
Dermal Exposure (with PPE)		**20**	mg a.s./ day	DE(PPE) = (1/PPE-factor) x DE
Internal exposure				
IA	Inhalation Absorption	100	%	
DA	Dermal Absorption	9	%	
	AOEL	05.sty	mg a.s./ day	based on 70 kg bw
		Without PPE	**With PPE**	
	Internal exposure	[mg a.s. / day]	[mg a.s. / day]	
	Inhalation	1,0000	1,0000	IE(int) = IE x (IA/100)
	Dermal	18,0000	1,8000	DE(int) = DE x (DA/100)
	Total	**19,0000**	**2,8000**	**sum**
	% AOEL			
	Inhalation	18	18	%AOEL = 100 x IE(int) / AOEL
	Dermal	321	32	%AOEL = 100 x DE(int) / AOEL
	Total	**339**	**50**	**sum**

A 3.1.3 Worker exposure: Low berries and other small fruits (strawberry) – AOEM model (indoor application)

Worker exposure from residues on foliage for Nordox 75 WG			
Crop type	Leaf vegetables and fresh herbs		
Indoor or outdoor	Indoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Number of applications	3		*i_AppNo*
Interval between multiple applications	7	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	2.6		*d_MAF*
Dermal absorption of the product	0.10%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	1.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm^2	*d_DFR*
Working hours	8	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	5800	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	2500	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	3.5834281	1.5445811	0.3583428	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0597238	0.0257430	0.0059724	
% of RVNAS	74.65%	32.18%	7.47%	

Worker exposure from residues on foliage for Nordox 75 WG			
Crop type	Low berries and other small fruits		
Indoor or outdoor	Indoor		
Application method	Spray application		
Application equipment	Vehicle-mounted		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and forearm		
Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Number of applications	3		*i_AppNo*
Interval between multiple applications	7	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	2,6		*d_MAF*
Dermal absorption of the product	0,10%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	1,00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm^2	*d_DFR*
Working hours	8	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	5800	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	3000	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	750	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	3,5834281	1,8534973	0,4633743	
Total systemic exposure per kg body weight (mg/kg bw/day)	0,0597238	0,0308916	0,0077229	
% of RVNAS	74,65%	38,61%	9,65%	

Worker exposure from residues on foliage for Nordox 75 WG			
Crop type	Low berries and other small fruits		
Indoor or outdoor	Indoor		
Application method	Spray application		
Application equipment	Vehicle-mounted		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and forearm		
Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Number of applications	3		*i_AppNo*
Interval between multiple applications	7	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	2,6		*d_MAF*
Dermal absorption of the product	1,00%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	9,00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm^2	*d_DFR*
Working hours	8	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	5800	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	3000	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	750	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	32,2508527	16,6814755	4,1703689	
Total systemic exposure per kg body weight (mg/kg bw/day)	0,5375142	0,2780246	0,0695061	
% of RVNAS	671,89%	347,53%	86,88%	

A 3.1.4 Worker exposure: Fruiting vegetables – AOEM model (indoor application)

Worker exposure from residues on foliage for Nordox 75 WG			
Crop type	Fruiting vegetables		
Indoor or outdoor	Indoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Number of applications	3		*i_AppNo*
Interval between multiple applications	7	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	2.6		*d_MAF*
Dermal absorption of the product	0.10%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	1.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm^2	*d_DFR*
Working hours	8	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	5800	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	2500	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	3.5834281	1.5445811	0.3583428	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0597238	0.0257430	0.0059724	
% of RVNAS	74.65%	32.18%	7.47%	

Worker exposure from residues on foliage for Nordox 75 WG			
Crop type	Fruiting vegetables		
Indoor or outdoor	Indoor		
Application method	Spray application		
Application equipment	Vehicle-mounted		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Number of applications	3		*i_AppNo*
Interval between multiple applications	7	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	2,6		*d_MAF*
Dermal absorption of the product	1,00%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	9,00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm^2	*d_DFR*
Working hours	8	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	5800	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	2500	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	32,2508527	13,9012296	3,2250853	
Total systemic exposure per kg body weight (mg/kg bw/day)	0,5375142	0,2316872	0,0537514	
% of RVNAS	671,89%	289,61%	67,19%	

A 3.1.5 Worker exposure: Leaf vegetables – AOEM model (indoor application)

Worker exposure from residues on foliage for Nordox 75 WG			
Crop type	Leaf vegetables and fresh herbs		
Indoor or outdoor	Indoor		
Application method	Downward spraying		
Application equipment	Vehicle-mounted		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Number of applications	3		*i_AppNo*
Interval between multiple applications	7	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	2.6		*d_MAF*
Dermal absorption of the product	0.10%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	1.00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm^2	*d_DFR*
Working hours	8	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	5800	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	2500	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	3.5834281	1.5445811	0.3583428	
Total systemic exposure per kg body weight (mg/kg bw/day)	0.0597238	0.0257430	0.0059724	
% of RVNAS	74.65%	32.18%	7.47%	

Worker exposure from residues on foliage for Nordox 75 WG			
Crop type	Leaf vegetables and fresh herbs		
Indoor or outdoor	Indoor		
Application method	Spray application		
Application equipment	Vehicle-mounted		
Worker's task	Reaching, picking		
Main body parts in contact with foliage	Hand and body		
Application rate of active substance	1	kg a.s./ha	*i_AppRate*
Number of applications	3		*i_AppNo*
Interval between multiple applications	7	days	*i_AppInt*
Half-life of active substance	30	days	*d_HalflifeAS*
Multiple application factor	2,6		*d_MAF*
Dermal absorption of the product	1,00%		*i_AbsorpProduct*
Dermal absorption of the in-use dilution	9,00%		*i_AbsorpInuse*
Dislodgeable foliar residue (i_AppRate*i_DFR)	3	µg a.s./cm^2	*d_DFR*
Working hours	8	hr	*d_WorkHr*
Dermal transfer coefficient - Total potential exposure	5800	cm^2/hr	*d_DermTcUCV*
Dermal transfer coefficient - arms, body and legs covered	2500	cm^2/hr	*d_DermTcCV1*
Dermal transfer coefficient - hands, arms, body and legs covered	580	cm^2/hr	*d_DermTcCV2*
Inhalation transfer coefficient for automated applications	NA	ha/hr*10^(-3)	*d_InhalTcAut*
Inhalation transfer coefficient for cutting ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcCut*
Inhalation transfer coefficient for sorting / bundling ornamentals	NA	ha/hr*10^(-3)	*d_InhalTcSort*

1. Total

	Potential exposure	Work wear - arms, body and legs covered	Working wear and gloves	Comments
Total systemic exposure (mg a.s./day)	32,2508527	13,9012296	3,2250853	
Total systemic exposure per kg body weight (mg/kg bw/day)	0,5375142	0,2316872	0,0537514	
% of RVNAS	671,89%	289,61%	67,19%	

Appendix 4 Detailed evaluation of exposure and/or DFR studies relied upon (KCP 7.2, KCP 7.2.1.1, KCP 7.2.2.1, KCP 7.2.3.1)

None.