REGISTRATION REPORT

Part B
Section 6
Mammalian Toxicology

Detailed summary of the risk assessment

Product code: ARY-0469-04
Product name(s): ASAHI MAX
Chemical active substance:
Sodium 5-nitroguaiacolate 3 g/L
Sodium o-nitrophenolate 6 g/L
Sodium p-nitrophenolate 9 g/L

Central Zone
Zonal Rapporteur Member State: Poland

CORE ASSESSMENT

Applicant: Asahi Chemical Europe s.r.o.
Submission date: June 2022
MS Finalisation date: March 2023 (initial Core Assessment)
June 2023 (final Core Assessment)

Version history

When	What
June 2022	Initial version of dRR for submission to zRMS
March 2023	Initial zRMS assessment The report in the dRR format has been prepared by the Applicant, therefore all comments, additional evaluations and conclusions of the zRMS are presented in grey commenting boxes. Minor changes are introduced directly in the text and highlighted in grey. Not agreed or not relevant information are ~~struck through and shaded for transparency~~.
June 2023	Final report (Core Assessment updated following the commenting period) No additional information or assessments after the commenting period.

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Reviewer general comments:

This dossier has been prepared to support registration of ARY-0469-04 as a plant growth regulator of winter wheat, oilseed rape and sugar beet in Poland and Zonal registration for which PL was designated zRMS.
Product was not a representative formulation reviewed during the Annex I inclusion/active substance renewal and there was no way to refer to the results of the studies evaluated in DAR (2007). Therefore, relevant data on the plant protection product ARY-0469-04 had to be generated for authorization.
Formulation ARY-0469-04 /ASAHI MAX has been already registered in Europe Southern Zone, (for details information see Table 6.1-1). For purpose of mentioned above registration, all toxicity studies has been evaluated and accepted at EU level by zRMS Greece according to Uniform Principles.

Thus, for current registration (Central Zone), zRMS PL takes into account accepted *in vivo* studies and do not request for new one. Based on studies outcome, PPP ASAHI MAX containing 3g/L sodium 5-nitroguaiacolate (Na 5-NG), 6 g/L sodium ortho-nitrophenolate (Na o-NP) and 9 g/L sodium para-nitrophenolate (Na p-NP)) has a low toxicity in respect to acute oral, dermal and inhalation toxicity and is not irritating to the xxxxxx skin. Whilst slight irritation was observed in the xxxxxx eye, this was insufficient to trigger classification. A skin sensitisation test (LLNA) confirmed that ASAHI MAX is not a skin sensitiser. Taking into account all submitted data and the labelling of the active substances, ASAHI MAX does not warrant hazard classification.
Detailed discussion regarding submitted studies is available in the Appendix 2, point A 2.1

NDE assessment for operator, workers and B&R exposure to the Na 5-NG (3 g/L), Na *o*-NP (6 g/L) and Na *p*-NP (9 g/L) considering all critical use(s) and all tasks, identify safe use of the product ARY-0469-04/ASAHI MAX.

Operator exposure:
The zonal assessment was based on the maximum product application rate of 0.2 kg/ha.
Summary of critical use patterns (worst cases):

Crop type	F	Equipment Application method	Maximum application rate kg product/ha (g a.s./ha)	Maximum volume water (L/ha)
Oil crops	F	Vehicle-mounted Downward spraying	0.2 L/ha Na 5-NG (0,6 g/ha) Na *o*-NP (1,2 g/ha) Na *p*-NP (1,8 g/ha)	500

thus, according to the EFSA Guidance calculations, a safe use could be demonstrated for operators using ARY-0469-04 /ASAHI MAX for proposed uses, even if no PPE is worn.

Worker exposure:
- according to the EFSA Guidance calculations and EUROPOEM II calculations, a safe use could be demonstrated for workers using ARY-0469-04 /ASAHI MAX for proposed uses, using only work wear.

Bystander and resident exposure:
- there is no undue risk to any resident after accidental short-term exposure to ARY-0469-04 /ASAHI MAX even if added are exposures of the three components.

6 Mammalian Toxicology (KCP 7)

6.1 Summary

Table 6.1-1: Information on ARY-0469-04/ASAHI MAX *

Product name and code	ARY-0469-04/ASAHI MAX
Formulation type	Soluble concentrate [Code: SL]
Active substance(s) (incl. content)	Sodium 5-nitroguaiacolate 3 g/L Sodium o-nitrophenolate 6 g/L Sodium p-nitrophenolate 9 g/L
Function	Plant growth regulator
Product already evaluated as the 'representative formulation' during the approval of the active substance(s)	As a representative formulation for approval of active substances was evaluated product ARY-0469-01 / ATONIK (in Poland registered as ASAHI SL): Sodium 5-nitroguaiacolate 1,0 g/L Sodium *o*-nitrophenolate 2,0 g/L Sodium *p*-nitrophenolate 3,0 g/L Product ASAHI MAX (in Greece registered as Atonik SL) is 3 time more concentrated product than ATONIK. There is no other difference.
Product previously evaluated in another MS according to Uniform Principles	Yes Greece: ATONIK SL (reg nº:8226; 23.07.2014)

* Information on the detailed composition of ARY-0469-04/ASAHI MAX 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 ARY-0469-04/ASAHI MAX according to Regulation (EC) No 1272/2008

Hazard class(es), categories:	--
Hazard pictograms or Code(s) for hazard pictogram(s):	--
Signal word:	--
Hazard statement(s):	--
Precautionary statement(s):	--
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, bystanders and residents for ARY-0469-04/ASAHI MAX

	Result	PPE / Risk mitigation measures
Operator outdoor	Acceptable	None
Workers outdoor	Acceptable	None
Bystanders	Acceptable	None
Residents	Acceptable	None

No unacceptable risk for workers was identified when the product is used as intended and provided that the PPE/ risk mitigation measures stated in Table 6.1-3 are applied.

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

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

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, bystander or resident 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 a) a.s. 1 b) a.s. 2**	**Water L/ha min / max**			**Operator**	**Worker**	**Bystander**	**Residents**
1	Winter oilseed rape (BBCH 29-69), mustard, spring rape, turnip rape, camelina, garden radish, poppy, linseed, hemp, sunflower, borage	F	spray	2 (7)	Na 5NG:0,6 Na oNP: 1,2 Na pNP: 1,8	200-500	28	Crops marked in ~~yellow~~ grey is registered as a minor crops on the base of art 51 (extrapolation from winter osr)				
2	Winter wheat (BBCH 21-49), spring rye, spelt, emmer wheat, small spelt, durum wheat	F	spray	1	Na 5NG:0,6 Na oNP: 1,2 Na pNP: 1,8	200-300	28	Crops marked in ~~yellow~~ grey is registered as a minor crops on the base of art 51 (extrapolation from winter wheat)				
3	Sugar beet (BBCH 12-49) fodder beet, red beet, swede, turnip	F	spray	2 (7)	Na 5NG:0,6 Na oNP: 1,2 Na pNP: 1,8	200-500	15	Crops marked in ~~yellow~~ grey is registered as a minor crops on the base of art 51 (extrapolation from sugar beet)				

* 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

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
No data gap.

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-.

Table 6.2-1: Information on active substance(s)

	Sodium 5-nitroguaiacolate	**Sodium *o*-nitrophenolate**	**Sodium p-nitrophenolate**
Common Name	Sodium 5-nitroguaiacolate	Sodium 2-nitrophenolate	Sodium 4-nitrophenolate
CAS-No.	67233-85-6	824-39-5	824-78-2
Classification and proposed labelling			
With regard to toxicological endpoints (according to the criteria in Reg. 1272/2008, as amended)	-Hazard classes (s), categories: Self-react. C; Eye Dam. 1; Acute Tox. 4; -Code(s) for hazard pictogram(s): GHS01; GHS05; GHS07 -Signal word: Danger -Hazard statement(s): H242, H318, H302	-Hazard classes (s), categories: Self-react. C; Eye Dam. 2; Acute Tox. 4; -Code(s) for hazard pictogram(s): GHS01; GHS05; GHS07 -Signal word: Danger -Hazard statement(s): H242, H319, H302	-Hazard classes (s), categories: Self-react. C; Eye Dam. 2; Acute Tox. 4; -Code(s) for hazard pictogram(s): GHS01; GHS05; GHS07 -Signal word: Danger -Hazard statement(s): H242, H319, H302
Additional C&L proposal	--	--	--
Agreed EU endpoints			
AOEL systemic	0.007 mg/kg bw/d	0.007 mg/kg bw/d	0.007 mg/kg bw/d
Reference	EFSA Scientific Report (2008) 191, 1-130	EFSA Scientific Report (2008) 191, 1-130	EFSA Scientific Report (2008) 191, 1-130
Conditions to take into account/critical areas of concern with regard to toxicology			
SANCO/210/08-rev.2 (17 May 2013)	For the implementation of the uniform principles of Annex VI, the conclusions of the review report on the Na 5-NG, Na *o*-NP and Na *p*-NP, and in particular Appendices I and II thereof, as finalised in the Standing Committee on the Food Chain and Animal Health on 17 May 2013 shall be taken into account. In this overall assessment: Member States must pay particular attention to: -the protection of the operators and workers safety. Authorised conditions of use must prescribe the application of adequate personal protective equipment and risk mitigation measures to reduce the exposure.		

6.3 Toxicological Evaluation of Plant Protection Product

A summary of the toxicological evaluation for ARY-0469-04/ASAHI MAX 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.

Table 6.3-1: Summary of evaluation of the studies on acute toxicity including irritancy and skin sensitisation for ARY-0469-04/ASAHI MAX

Type of test, species, model system (Guideline)	**Result**	**Acceptability***	**Classification (acc. to the criteria in Reg. 1272/2008)**	**Reference**
LD_{50} oral, rat (US EPA81-1; EU test method B.1)	>5000 mg/kg bw	No	None	Xxxxxx., (1990)
LD_{50} oral, rat (OECD 423)	>2000 mg/kg bw	Yes	None	Xxxxxx(2009a)
LD_{50} dermal, rat (USE EPA 81-2;	> 2000 mg/kg bw	Supplementary	None	Xxxxxx, S.R., (1985a)

OECD 402)				
LD_{50} dermal, xxxxxx (USE EPA 81-2; OECD 402)	> 2000 mg/kg bw	Supplementary	None	Xxxxxx, (1985b)
LD_{50} dermal, rat (OECD 402)	> 2000 mg/kg bw	Yes	None	Xxxxxx(2009b)
LC_{50} inhalation, rat (USE EPA 81-3; OECD 403)	> 6.7 mg/L air/4h	No	None	Xxxxxx, (1990)
LC_{50} inhalation, rat (OECD 403)	> 5.02 mg/L air	Yes	None	Xxxxxx (2009)
Skin irritation, xxxxxx (US EPA 158.135 81-5. OECD 404)	Non-irritant	No	None	Xxxxxx., (1984a)
Skin irritation, xxxxxx (OECD 404)	Non-irritant	Yes	None	Xxxxxx(2009c)
Eye irritation, xxxxxx (US EPA 158.135 81-4. OECD 405)	Non-irritant	No	None	Xxxxxx., (1984b)
Eye irritation, xxxxxx (OECD 405)	Slightly irritant	Yes	None	Xxxxxx(2009d)
Skin sensitisation, mouse (OECD 429, LLNA)	Non-sensitising	Yes	None	Xxxxxx (2010)
Supplementary studies for combinations of plant protection products	No data – not required			

***** Detailed discussion regarding submitted studies is available in the Appendix 2, point A 2.1

Table 6.3-2: Additional toxicological information relevant for classification/labelling of ARY-0469-04/ASAHI MAX

	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)	Sodium 5-nitroguaiacolate CAS 67233-85-6 0.3% w/w	Self-react. C; H242 Acute Tox. 4; H302 Eye Dam 1; H318	Reg. 1272/2008/ MSDS	None
Toxicological properties of active substance(s) (relevant for classification of product)	Sodium o-nitrophenolate CAS 824-39-5 0.6% w/w	Self-react. C; H242 Acute Tox. 4; H302 Eye Irrit. 2; H319	Reg. 1272/2008/ MSDS	None
Toxicological properties of active substance(s) (relevant for classification of product)	Sodium p-nitrophenolate CAS 824-78-2 0.9% w/w	Self-react. C; H242 Acute Tox. 4; H302 Eye Irrit. 2; H319	Reg. 1272/2008/ MSDS	None
Toxicological properties of non-active substance(s) (relevant for classification of product)	--	--	--	--
Further toxicological information	No data – not required	--	--	--

* Please use concentration range or concentration limit (e.g. 1-10 % or > 1 %) as provided in MSDS.
** Material safety data sheet by the applicant

6.4 Toxicological Evaluation of Groundwater Metabolites

PECgw calculations after leaching from soil for metabolite M5 were performed (see Part B, Section 8, chapter 8). All 80th percentiles at 1 m soil depth ((µg/L) were estimated to be lower than 0.1 µg/L. Therefore, no further assessment is necessary.

All metabolite concentrations are predicted to stay below 0.1 µg/L-no groundwater assessment is required.

6.5 Dermal Absorption (KCP 7.3)

A summary of the dermal absorption rates for the active substances in ARY-0469-04 /ASAHI MAX are presented in the following table.

Table 6.5-3: Dermal absorption rates for active substances in ARY-0469-04 /ASAHI MAX

	Sodium p-nitrophenolate / CAS 824-78-2		Sodium 5-nitroguaiacolate / CAS 67233-85-6		Sodium o-nitrophenolate / CAS 824-39-5	
	Value	**Reference**	**Value**	**Reference**	**Value**	**Reference**
Concentrate (3 g/L)	8 %	Craig BSc S., 2012	8 %	Craig BSc S., 2012*	8 %	Craig BSc S., 2012*
Dilution (0.0015 g/L)	27 %	Craig BSc S., 2012	27 %	Craig BSc S., 2012*	27 %	Craig BSc S., 2012*

*considering that the *in vitro* study Craig BScS. (2012), carried out with sodium p-nitrophenolate is applicable to the active substance Sodium 5-nitroguaiacolate and Sodium o-nitrophenolate, that all three substances are equivalent given their close structural similarity and similar physic-chemical properties.

6.5.1 Justification for proposed values – Sodium p-nitrophenolate

Proposed dermal absorption rates for Sodium p-nitrophenolate are based on dermal absorption studies on a formulation to Atonik (SL). The study results are summarized in the following table. Full summaries of studies on the dermal absorption of Sodium p-nitrophenolate /Atonik that have not previously been evaluated within an EU peer review process are described in detail in 0.

Table 6.5-2: Summary of the results of submitted dermal absorption studies for Sodium p-nitrophenolate

Test	Concentrate (3 g/L)	Spray dilution (0.0015 g/l)	Formulation in study	Acceptability of study	Justification provided on representativity of study formulation for current product	Acceptability of justification	Reference
In vitro (human)	8%	27%	ATONIK (Sodium 5-nitroguaiacolate, 0.1% and Sodium o-nitrophenolate 0.2% and Sodium p-nirophenolate 0.3%, SL)	Yes	Not required	Not applicable	Craig BSc S., 2012*

*considering that the *in vitro* study Craig BScS. (2012), carried out with sodium p-nitrophenolate is applicable to the active substance Sodium 5-nitroguaiacolate and Sodium o-nitrophenolate, that all three substances are equivalent given their close structural similarity and similar physic-chemical properties.

6.6 Exposure Assessment of Plant Protection Product (KCP 7.2)

Table 6.6-5: Product information and toxicological reference values used for exposure assessment

Product name and code	ARY-0469-04/ASAHI MAX			
Formulation type	Soluble concentrate (SL)			
Category	Plant growth regulator			
Container size(s), short description	HDPE bottles of 50 ml (cylindrical / approx. 44 mm diameter x 72 mm), 200 ml (type A: cylindrical / approx. 51 mm diameter x 146 mm; type B: cylindrical / approx. 54 mm diameter x 138 mm), 500 mL (type A: cylindrical / approx. 76,2 mm diameter x 168,5 mm; type B: cylindrical / approx. 69 mm diameter x 187 mm) and 1 L (cylindrical / approx. 89 mm diameter x 238 mm) HDPE canister of 5 (round square / approx. 142 mm depth x 193 mm width x 305 mm height) and 10 L (round square / approx. 179 mm depth x 240 mm width x 375 mm height) HDPE canister of 20 L (round square / approx. 245 mm depth x 293 mm width x 400 mm height)			
Active substance(s) (incl. content)	Sodium 5-nitroguaiacolate 3 g/L Sodium o-nitrophenolate 6 g/L Sodium p-nitrophenolate 9 g/L			
AOEL systemic	Sodium 5-nitroguaiacolate 0.007 mg/kg bw/d Sodium o-nitrophenolate 0.007 mg/kg bw/d Sodium p-nitrophenolate 0.007 mg/kg bw/d			
Inhalation absorption	100 %			
Oral absorption	>80%			
Dermal absorption		Sodium 5-nitroguaiacolate	Sodium o-nitrophenolate	Sodium p-nitrophenolate
	Concentrate	8%	8%	8%
	Spray dilution	27%	27%	27%

6.6.1 Selection of critical use(s) and justification

The critical GAP(s) used for the exposure assessment of the plant protection product are shown in Table 6.1-4. A list of all intended uses within the Central Zone is given in Part B, Section 0.

Justification
The critical GAP for crops reflects the worst case is for the maximum application rate, with the highest number of applications.

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 ARY-0469-04/ ASAHI MAX according to the critical use is presented in Table 6.6-2. Outcome of the estimation is presented in Table 6.6-3. Detailed calculations are in 0.

Table 6.6-6: Exposure models for intended uses

Critical use	Oilseed rape (max. 0.2 L product/ha (0.6 g Na 5-NG + 1.2 g Na o-NP + 1.8 Na p-NP) Downward spraying, vehicle mounted.
Model(s)	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

It should be noted that the product is a mixture of three active substances. For pesticide formulations containing two or more active substances, combined toxicity and their potential relevance for the risk assessments should be considered (see point 6.6.5)

Table 6.6-3: Estimation of operator exposure

Model	Level of PPE	Active substance	Total absorbed dose (mg/kg/day)	% of systemic AOEL	∑%AOEL
Tractor mounted. Low crop. Oilseed rapes Application rate: 0.2 l/ha (0.6 g Na 5NG/ha; 1.2 g Na oNP /ha; 1.8 g Na pNP/ha)					
EFSA 2014-Model Body weight: 60 Kg	Potential exposure	Na 5NG	0.0008984	12.83	63.2%
		Na oNP	0.0014993	21.42	
		Na pNP	0.0020266	28.95	
	Work wear-arms, body and legs covered	Na 5NG	0.0004845	6.92	34.69%
		Na oNP	0.0008219	11.74	
		Na pNP	0.0011223	16.03	

According to the EFSA Guidance, the systemic exposure of operators in oilseed rapes (cover winter wheat and sugar beet) during tractor-mounted boom sprayer application in downward spraying using ARY-0469-04/ASAHI MAX for proposed uses results in 0.0008984 mg/kg bw/day of Na 5NG, 0.0014993 mg/kg bw/day of Na oNP and 0.0020266 mg/kg bw/day of Na pNP, without the use of personal protective equipment (potential exposure). The values correspond to 12.83%, 21.42% and 28.95% of the AOEL (0.007 mg/kg bw/day) of Na 5NG, Na oNP and Na pNP, respectively. And the combined exposure is of 63.2%, below 100%. Therefore, the risk of a combined operator exposure is acceptable.

Conclusion
Thus, according to the EFSA Guidance calculations, a safe use could be demonstrated for operators using ARY-0469-04 /ASAHI MAX for proposed uses, even if no PPE is worn.

6.6.3 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.

6.6.4 Worker exposure (KCP 7.2.3)

6.6.4.1 Estimation of worker exposure

Table 6.6-4 shows the exposure models used for estimation of worker exposure after entry into a previously treated area or handling a crop treated with ARY-0469-04/ ASAHI MAX according to the critical uses. Outcomes of the estimation are presented in Table 6.6-5. Detailed calculations are in 0.

Table 6.6-4: Exposure models for intended uses

Critical uses	Oilseed rape (2 applications x 0.2 L product/ha)
Models	- EFSA calculator: 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 - Europoem II (worker model) (according central zone requirements rev 2021-06-1 for Poland)

Worker exposure according EFSA model

Table 6.6-5: Estimated worker exposure –EFSA model

Model	Level of PPE	Active sub-stance	Total absorbed dose (mg/kg/day)	% of systemic AOEL	∑%AOEL
Re-entry Oilseed rapes Application rate: 0.2 l/ha (0.6 g Na 5NG/ha; 1.2 g Na oNP /ha; 1.8 g Na pNP/ha) Nº applications: 2 Interval between applications: 7 days					
EFSA Guidance 2014	Potential exposure	Na 5NG	0.0003748	5.35	32.12%

Inspection and irrigation Work rate: 2 hours DT50: 30 days DFR: 3 µg/cm²/kg a.s./ha Body weight: 60 Kg	TC= 12.500 cm²/h	Na oNP	0.0007495	10.71	
		Na pNP	0.0011243	16.06	
	Work wear-arms, body and legs covered TC = 1400 cm²/h	Na 5NG	0.0000420	0.6	3.6%
		Na oNP	0.0000839	1.20	
		Na pNP	0.0001259	1.80	

According to the EFSA Guidance, the systemic exposure of workers during re-entry at oilseed rape (cover winter wheat and sugar beet) using ARY-0469-04/ASAHI MAX for proposed uses results in 0.0003748 mg/kg bw/day of Na 5NG, 0.0007495 mg/kg bw/day of Na oNP and 0.0011243 mg/kg bw/day of Na pNP, without the use of personal protective equipment (potential exposure). The values correspond to 5.35%, 10.71% and 16.06% of the AOEL (0.007 mg/kg bw/day) of Na 5NG, Na oNP and Na pNP, respectively. And the combined exposure is of 32.12%, below 100%. Therefore, the risk of a combined worker exposure is acceptable.

Conclusion
Thus, according to the EFSA Guidance calculations, a safe use could be demonstrated for workers using ARY-0469-04 /ASAHI MAX for proposed uses, even if no PPE is worn.

Worker exposure according EUROPOEM II model

Table 6.6-6: Estimated worker exposure –Europoem II model

Model	Level of PPE	Active sub-stance	Total absorbed dose (mg a.s/day)	% of systemic AOEL	∑%AOEL
Re-entry Winter wheat Application rate: 0.2 l/ha (0.6 g Na 5NG/ha; 1.2 g Na oNP /ha; 1.8 g Na pNP/ha) Nº applications: 1					
Europoem II Inspection and irrigation Work rate: 2 hours DFR: 3 µg/cm²/kg a.s./ha Body weight: 60 Kg	Work wear-arms, body and legs covered TC= 0.25 m²/h (field)	Na 5NG	0.002	1	4%
		Na oNP	0.005	1	
		Na pNP	0.007	2	

According central zone requirements (rev. 2021-06-1) for Poland, EUROPOEM II model is preferred for worker exposure for single uses per season. The systemic exposure of workers during re-entry at winter wheat using ARY-0469-04/ASAHI MAX for proposed uses results in 0.002 mg/day of Na 5NG, 0.005 mg/day of Na oNP and 0.007 values correspond to 1%, 1% and 2% of the AOEL (0.007 mg/kg bw/day) of Na 5NG, Na oNP and Na pNP, respectively. And the combined exposure is of 4%, below 100%. Therefore, the risk of a combined worker exposure is acceptable.

Conclusion
Thus, according to the EUROPOEM II calculations, a safe use could be demonstrated for workers using ARY-0469-04 /ASAHI MAX for proposed uses, using only work wear.

6.6.4.2 Refinement of generic DFR value (KCP 7.2)

It is not required.

6.6.4.3 Measurement of worker exposure

Since the worker exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) will not be exceeded under conditions of intended uses and considering of use if no PPE is worn, a study to provide measurements of worker exposure was not necessary and was therefore not performed.

6.6.5 Bystander and resident exposure (KCP 7.2.2)

6.6.5.1 Estimation of bystander and resident exposure

No bystander risk assessment is required for PPPs that do not have significant acute toxicity or the potential to exert toxic effects after a single exposure. Exposure in this case will be determined by average exposure over a longer duration, and higher exposures on one day will tend to be offset by lower exposures on other days. Therefore, exposure assessment for residents also covers bystander exposure.

Table 6.6-7 shows the exposure models used for estimation of resident exposure to product ARY-0469-04 /ASAHI MAX in oilseed rape. Outcome of the estimation is presented in Table 6.6-8. (longer term resident exposure). Detailed calculations are in 0.

Table 6.6-7: Exposure models for intended uses

Critical uses	Oilseed rape (2 applications x 0.2 l/ha (0.6 g Na 5NG/ha; 1.2 g Na oNP /ha; 1.8 g Na pNP/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 6.6-8: Estimated resident exposure

Tractor mounted boom spray application outdoors to low crops (oilseed rape)
Buffer zone: 2-3 (m)
Drift reduction technology: no
DT_{50}: 30 days; DFR: 3 µg/cm^2/kg a.s./ha
Number of applications and application rate: 2 x 0.2 l/ha (0.6 g Na 5NG/ha; 1.2 g Na oNP /ha; 1.8 g Na pNP/ha)
Interval between treatments: 7 days

Model data	Active substance	Spray drift (75 th percentile)	Vapour (75 th percentile)	Surface deposits (75 th percentile)	Entry into treated crops (75 th percentile)	All pathways (mean)
EFSA 2014 Resident Children	**Total absorbed dose (mg/kg bw /day)**					
	Na 5NG	0.00002	0.0011	0.0000053	0.000051	0.001126
	Na oNP	0.0000436	0.001070	0.0000105	0.0001012	0.0011824
	Na pNP	0.0000654	0.001070	0.0000158	0.0001518	0.0012386
	% of systemic AOEL					
	Na 5NG	0.31%	15.29%	0.08%	0.72%	16.09%
	Na oNP	0.62%	15.29%	0.15%	1.45%	16.89%
	Na pNP	0.93%	15.29%	0.23%	2.17%	17.69%
	∑ % AOEL	1.86%	45.87%	0.46%	4.34%	**50.67%**
EFSA 2014 Resident Adult	**Total absorbed dose (mg/kg bw /day)**					
	Na 5NG	0.000005	0.00023	0.000002	0.000028	0.0002564
	Na oNP	0.0000104	0.00023	0.0000041	0.0000562	0.0002828
	Na pNP	0.000156	0.000230	0.0000061	0.0000843	0.0003091
	% of systemic AOEL					
	Na 5NG	0.07%	3.29%	0.03%	0.40%	3.66%
	Na oNP	0.15%	3.29%	0.06%	0.80%	4.04%
	Na pNP	0.22%	3.29%	0.09%	1.20%	4.42%
	∑ % AOEL	0.44%	9.87%	0.18%	2.4%	**12.12%**

Results

According to the EFSA Guidance, the total estimated systemic residential exposure, in % of systemic AOEL (all pathways (mean)) of children and adults, correspond to 16.09% and 3.66% of the AOEL of Sodium 5-nitroguaiacolate, respectively for application in oilseed rape (downward spraying).
According to the EFSA Guidance, the total estimated systemic residential exposure, % of systemic AOEL (all pathways (mean)) of children and adults, correspond to 16.89% and 4.04% of the AOEL of Sodium o-nitrophenolate, respectively for application in oilseed rape (downward spraying).
According to the EFSA Guidance, the total estimated systemic residential exposure, % of systemic AOEL (all pathways (mean)) of children and adults, correspond to 17.69% and 4.42% of the AOEL of Sodium p-nitrophenolate, respectively for application in oilseed rape (downward spraying).
The systemic combined exposure of residents of the three components using ARY-0469-04/ASAHI MAX for proposed uses results in 50.67% of the AOEL for children and 12.12% of the AOEL for adults (all

pathways (mean)). Therefore, the risk of a combined resident exposure is acceptable.

Conclusion
It is concluded that there is no undue risk to any resident after accidental short-term exposure to ARY-0469-04 /ASAHI MAX even if we add exposures of the three components. This has no labelling implications.

6.6.5.2 Measurement of bystander and/or resident exposure

Since the resident exposure estimations carried out indicated that the acceptable operator exposure level (AOEL) for Sodium 5-nitroguaiacolate, Sodium o-nitrophenolate and Sodium p-nitrophenolate, will not be exceeded under conditions of intended uses and considering above mentioned risk mitigation measures, a study to provide measurements of resident/bystander exposure was not necessary and was therefore not performed.

6.6.6 Combined exposure

The product is a mixture of three active substances. For pesticide formulations containing two or more active substances, combined toxicity and their potential relevance for the risk assessments should be considered.

According the *Conclusion on the peer review of sodium 5-nitroguaiacolate, sodium o-nitrophenolate and sodium p-nitrophenolate. EFSA Scientific Report (2008) 191, 1-130,* the exposure assessment should consider the three active substances contained in 'Asahi Max' (Na 5-NG, Na *o*-NP and Na *p*-NP) and the exposure estimates for the individual active substances should be added. This approach is supported by the EFSA.
Furthermore, the three active substances (Na 5-NG, Na *o*-NP and Na *p*-NP), have the same primary target organ (kidney), so we consider that it´s necessary to calculate the combined exposure.

6.6.6.1 Exposure assessment of Sodium 5-nitroguaiacolate, Sodium o-nitrophenolate and Sodium p-nitrophenolate in ARY-0469-04 /ASAHI MAX

Note: The combined toxicological effect of these active substances has not been investigated with regard to repeated dose toxicity.

At the first tier, combined exposure is calculated as the sum of the component exposures without regard to the mode of action or mechanism/target of toxicity. Initially, the individual Hazard Quotients (HQ) are calculated for all active substances in the PPP by assessing the exposure according to appropriate models and dividing the individual exposure levels by the respective systemic AOEL. This is equivalent to the predicted exposure as % of systemic AOEL from table 6.6-9 converted to decimal. The Hazard Index (HI) is the sum of the individual HQs.

Table 6.6-9: Risk assessment from combined exposure (worst case)

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Operators –Oilseed rape (Low crops) Tractor mounted application spray application Potential exposure (without PPE)	Sodium 5-nitroguaiacolate	0.1283
	Sodium *o*-nitrophenolate	0.2142
	Sodium *p*-nitrophenolate	0.2895
	Cumulative risk operators (HI)	**0.632**
Workers-oilseed rape (inspection and irrigation) Potential exposure (without PPE)	Sodium 5-nitroguaiacolate	0.0535
	Sodium *o*-nitrophenolate	0.1071
	Sodium *p*-nitrophenolate	0.1606
	Cumulative risk operators (HI)	**0.3212**

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
Resident - child Buffer zone: 2-3 m	Sodium 5-nitroguaiacolate	
	Drift	0.0031
	Vapour	0.1529
	Deposits	0.0008
	Re-entry	0.0072
	Sum of all pathways	0.1609
	Sodium *o*-nitrophenolate	
	Drift	0.0062
	Vapour	0.1529
	Deposits	0.0015
	Re-entry	0.0145
	Sum of all pathways	0.1689
	Sodium *p*-nitrophenolate	
	Drift	0.0093
	Vapour	0.1529
	Deposits	0.0023
	Re-entry	0.0217
	Sum of all pathways	0.1769
	Cumulative risk resident – child (HI)	
	Drift	**0.0186**
	Vapour	**0.4587**
	Deposits	**0.0046**
	Re-entry	**0.0434**
	Sum of all pathways	**0.5067**
Resident – adult Buffer zone: 2-3 m	Sodium 5-nitroguaiacolate	
	Drift	0.0007
	Vapour	0.0329
	Deposits	0.0003
	Re-entry	0.0040
	Sum of all pathways	0.0366
	Sodium *o*-nitrophenolate	
	Drift	0.0015
	Vapour	0.0329
	Deposits	0.0006
	Re-entry	0.0080
	Sum of all pathways	0.0404
	Sodium *p*-nitrophenolate	
	Drift	0.0022
	Vapour	0.0329
	Deposits	0.0009

Application scenario	Active ingredient	Estimated exposure / AOEL (HQ)
	Re-entry	0.0012
	Sum of all pathways	0.0442
	Cumulative risk resident – child (HI)	
	Drift	**0.0044**
	Vapour	**0.0987**
	Deposits	**0.0018**
	Re-entry	**0.024**
	Sum of all pathways	**0.1212**

The Hazard Index is < 1. Thus, combined exposure to both active substances in ARY-0469-04/ASAHI MAX is not expected to present a risk for operators, workers, residents and bystanders. No further refinement of the assessment is required.

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**	Vertebrate study Y/N	Owner
KCP 7.1.1/02	xxxxx	2009a	Acute oral toxicity (acute toxic class method) with Atonik plus (1.8%) Bioservice Scientific Laboratories GmbH Asahi Chemical Europe s.r.o. Report no.: 083569 GLP, Unpublished	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.2/03	xxxxx	2009b	Acute dermal toxicity (limit) with Atonik plus (1.8%) Bioservice Scientific Laboratories GmbH Asahi Chemical Europe s.r.o. Report no.: 083570 GLP, Unpublished	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.3/02	xxxxx	2009	Atonik Plus (1.8%): Acute inhalation toxicity study in rats Eurofins Product Safety Laboratories, Asahi Chemical Europe s.r.o. Report no.: 26838 GLP, Unpublished	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.4/02	xxxxx	2009c	Acute dermal irritation/corrosion with Atonik Plus (1.8%) Bioservice Scientific Laboratories GmbH Asahi Chemical Europe s.r.o. Report no.: 090348 GLP, Unpublished	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.5/02	xxxxx	2009d	Acute eye irritation/corrosion with Atonik Plus (1.8%) Bioservice Scientific Laboratories GmbH Asahi Chemical Europe s.r.o. Report no.: 083573 GLP, Unpublished	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.6/01	xxxxx	2010	Test of Sensitisation (Local Lymph Node Assay – LLNA) with ATONIK PLUS (1.8%) BSL BIOSERVICE Scientific Latoratories GmbH, Germany Report no. 083574 GPL: Yes Unpublished	Y	Asahi Chemical Europe s.r.o.
KCP 7.3.1/01	Craig BSc, S.	2012	Sodium p-nitrophenolate: The *In Vitro* Percutaneous absorption of Radiollabelled Pesticide in the Concentrate and a Single In-Use Spray Dilution Through Human Skin. Charles River Test Facility Study Nº 791509, Report no. 33044 GPL: Yes	N	Asahi Chemical Europe s.r.o.

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
			Unpublished		

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	Vertebrate study Y/N	Owner
KCP 7.1.1/01	xxxxx	1990	Acute Exposure Oral Toxicity in Rats (Atonik) Pharmakon Research International. Inc.. Waverly. Pennsylvania 1841. USA PH 402-AH-004-90 GLP. not published	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.2/01	xxxxx	1985a	Acute dermal toxicity in rats (Atonik). Huntingdon Research Centre Ltd.. P.O. Box 2. Huntingdon. Cambridgeshire. PE18 6ES. England HRC Report No 85433D/ ACM 11/AC GLP. not published	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.2/02	xxxxx	1985b	Acute dermal toxicity in xxxxxxs (Atonik). Huntingdon Research Centre Ltd.. P.O. Box 2. Huntingdon. Cambridgeshire. PE18 6ES. England HRC Report No 85434D/ ACM 12/AC GLP. not published	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.3/01	xxxxx	1990	Atonik solution: Acute Inhalation Toxicity Study in Rats 4-hour Exposure Huntingdon Research Centre Ltd.. P.O. Box 2. Huntingdon. Cambridgeshire. PE18 6ES. England HRC Report No ACM 14/85584 GLP. not published	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.4/01	xxxxx	1984a	Irritant effects on xxxxxx skin (Atonik) Huntingdon Research Centre Ltd.. P.O. Box 2. Huntingdon. Cambridgeshire. PE18 6ES. England HRC Report No 84642D/ACM 7/SE GLP. not published	Y	Asahi Chemical Europe s.r.o.
KCP 7.1.5/01	xxxxx	1984b	Irritant effects on the xxxxxx eye (Atonik) Huntingdon Research Centre Ltd.. P.O. Box 2. Huntingdon. Cambridgeshire. PE18 6ES. England HRC Report No 84696D/ACM 8/SE(G) GLP. not published	Y	Asahi Chemical Europe s.r.o.

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
-	-	-	-	-	-

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
-	-	-	-	-	-

Appendix 2 Detailed evaluation of the studies relied upon

A 2.1 Statement on bridging possibilities

Comments of zRMS:	There are two sets of *In vivo* studies submitted by the Applicant to support registration of the product ARY-0469-04/ASAHI MAX. Following studies: LD_{50} oral, rat - xxxxxxxxxx., (1990) LC_{50} inhalation, rat xxxxxxxxxxx (1990) Skin irritation, xxxxxx xxxxxxxxxx (1984a) Eye irritation, xxxxxx xxxxxxxx (1984b), has been conducted with formulation ARY-0469-01/ATONIK which was representative formulation. Although the mentioned above studies was evaluated in the DAR 2007 and accepted but for current registration are not valid due to the difference in composition between reference formulation and registered one which contains different amount of active substance. (refer Part C). zRMS pointed out that inhalation toxicity study Xxxxxx, (1990) is not accepted due to the important limitation: - No information is provided concerning the content of the Atonik solution tested. - The nominal concentration of the test atmosphere was not reported. Studies: LD_{50} dermal, rat - xxxxxx (1985a) LD_{50} dermal, xxxxxx xxxxxxxx (1985b) were evaluated and accepted in the DAR 2007, because tested material has the same content of the active substance as in the formulation submitted for registration thus both studies can be considered as supportive for the ongoing registration assessment. Finally for actual registration of the product ARY-0469-04/ASAHI MAX second set of data has been accepted as a valid (see below): LD_{50} oral, rat, xxxxxxxxx (2009a) LD_{50} dermal, rat, xxxxxxxxxxx. (2009b) LC_{50} inhalation, rat, xxxxxxxxx. (2009) Skin irritation, xxxxxx, xxxxxxxx. (2009c) Eye irritation, xxxxxx, xxxxxxxx. (2009d) Skin sensitization, mouse, xxxxxxxxx (2010) Note: mentioned above studies has been previously evaluated at EU level by zRMS Greece according to Uniform Principles.

No new study is submitted.

A 2.2 Acute oral toxicity (KCP 7.1.1)

A 2.2.1 Study 1

Comments of zRMS:	Study xxxxxxxxxxx. 1990 has been evaluated and accepted in the DAR (2007), however study is not valid for the current registration due to differences in composition between the reference formulation (ARY-0469-01) and the formulation submitted for registration ARY-0469-04

~~The following study was performed to provide guideline compliant data for the endpoint acute oral toxicity in accordance with the requirements of Commission Regulation (EU) No 284/2013 and has been assessed and accepted at EU level for the inclusion of the Sodium nitrocompounds Na 5-NG, Na *o*-NP and Na *p*-NP in Annex I of Directive 91/414/EEC.~~

~~Reference~~	~~**KCP 7.1.1/01**~~
~~Report~~	~~xxxxxxxxx. 1990. Acute exposure oral toxicity – PH 402-AH-004-90 -Atonik Lot #158B0~~
~~Guideline(s)~~	~~US EPA Guideline 158.135. 81-1.; EU test method B.1~~

	The purity of the test formulation was not reported. This deviation did not affect the quality or the integrity of the results obtained.
Deviations	No
Previous evaluation:	Yes, evaluated and accepted in the DAR (2007)
GLP	Yes: in compliance with the Principles of Good Laboratory Practices (GLP) and meets the requirements from 40 CFR Part 160.
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-04/Atonik SL (Atonik Lot #158B0)
Species	Rat, Sprague-Dawley
No. of animals (group size)	5 males and 5 females
Dose(s)	Range finding: 500, 3200, 5000 mg/kg Limit test: 5000 mg/kg
Exposure	Range finding: orally Limit test: Once by gavage
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 1: Results of acute oral toxicity study in rats of ARY-0469-04/Atonik SL*

Dose (mg/kg bw)	**Toxicological results ***	**Duration of signs**	**Time of death**	**LD_{50} (mg/kg bw) (14 days)**
Male rats				
5000	0/0/5	0	-	> 5000
Female rats				
5000	0/0/5	0	-	> 5000

* ARY-0469-04/Atonik SL (Sodium 5-nitroguaiacolate 3 g/L, Sodium o-nitrophenolate 6 g/L, Sodium p-nitrophenolate 9 g/L); in GR registered (Reg. no: 8226 from 30.7.2014)

Table A 2: Summary of findings of acute oral toxicity study in rats of ARY-0469-04/Atonik SL

Mortality	No mortality occurred.
Clinical signs	Range finding study: piloerection was observed at the 3200 and 5000 mg/kg dose levels. Limit test: no signs were observed in any animals.
Body weight	The weight variation in animals used did not exceed +/- 20% of the mean weight for each sex.
Macroscopic examination	Terminal necropsy of the animals in the limit test revealed no visible lesions.

Conclusion

Under the experimental conditions, the oral LD_{50} of ARY-0469-04/Atonik SL is higher than 5000 mg/kg bw in rats. Thus, no classification for acute oral toxicity is required according to Regulation (EC) No. 1272/2008.

A 2.2.2 Study 2

Comments of zRMS:	Study *Acute oral toxicity (acute toxic class method)* Xxxxxx(2009a) has been previously evaluated at EU level by zRMS Greece according to Uniform Principles. Study was accepted. Outcome of the study still is valid for the current registration. Under experimental conditions the oral LD_{50} of the ARY-0469-04 is higher than 2000 mg/kg in rats thus, no classification for acute oral toxicity is required according to Regulation (EC) No. 1272/2008.

The following study was performed to provide guideline compliant data for the endpoint acute oral toxicity in accordance with the requirements of Commission Regulation (EU) No 284/2013 and before the implementation of Regulation 1107/2009. This study has not been assessed at EU level.

Reference	**KCP 7.1.1/02**
Report	Xxxxxx(2009a). Acute oral toxicity (acute toxic class method) with ATONIK PLUS (1.8%). Unpublished report no.: 083569
Guideline(s)	OECD 423
Deviations	No
Previous evaluation:	No
GLP	Yes (certificate laboratory)
Acceptability	Yes
Duplication (if vertebrate study)	Yes (The following study was performed before the implementation of Regulation 1107/2009)

Study dates: 13 January 2009 to 29 January 2009

Material and Methods

Test material (Lot/Batch No.)	ARY-0469-04/Atonik Plus (1.8%) (batch Nº 04I8)
Species	Rat. Wistar
No. of animals (group size)	6 females
Dose(s)	2000 mg/kg
Exposure	Once by gavage using an intubation cannula
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Table A3: Results of acute oral toxicity study in rats of ARY-0469-04/ ATONIK PLUS (1.8%)

Dose (mg/kg)	Toxicological results*	Duration of signs	Time of death	LD_{50} (mg/kg) (14 days)
2000	0/0/6	-	-	>2000

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 4: Summary of findings of acute oral toxicity study in rats of ARY-0469-04/ ATONIK PLUS (1.8%)

Mortality	No mortality occurred.
Clinical signs	No clinical signs were observed during the study
Body weight	The body weight gain of females was not affected by treatment with the test substance.
Macroscopic examination	Macroscopic examination revealed no apparent abnormalities in all the animals.

Conclusion/endpoint:
Under the experimental conditions, the oral LD_{50} of the ARY-0469-04 / ATONIK PLUS (1.8%) is higher than 2000 mg/kg in rats. Thus, no classification for acute oral toxicity is required according to Regulation (EC) No. 1272/2008.

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

A 2.3.1 Study 1

Comments of zRMS:	Study *Acute dermal toxicity to rats*, xxxxxx 1985a has been previously evaluated and accepted at EU level in the DAR (2007) by RMS Greece. Because tested formulation has the same content of the active substance as in the formulation submitted for current zonal registration thus, outcome of the study can be considered as supportive for the ongoing registration assessment.

The following acute dermal toxicity studies with rats were performed to provide guideline compliant data for the endpoint acute dermal toxicity in accordance with the requirements of Commission Regulation (EU) No 284/2013 and have been assessed and accepted at EU level for the inclusion of the Sodium nitrocompounds Na 5-NG, Na *o*-NP and Na *p*-NP in Annex I of Directive 91/414/EEC.

Reference	**KCP 7.1.2/01**
Report	xxxxxxxxxxx1985a. Acute dermal toxicity to rats of Atonik solution - HRC Report No 85433D/ ACM 11/AC
Guideline(s)	Yes/ US EPA Guideline 158.135. 81-2. OECD guideline 402
Deviations	No control test was performed. The batch No. and stability of the test substance were not reported
Previous evaluation:	Yes, evaluated and accepted in the DAR (2007)
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-04 /Atonik SL (Lot: not reported.)
Species	Rat. HC/CFY (remote Sprague-Dawley)
No. of animals (group size)	5 males + 5 females
Dose(s)	2000 mg/kg bw
Exposure	24 hours (dermal)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 5: Results of acute dermal toxicity study in rats of ARY-0469-04 /Atonik SL**

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Male rats				
2000	0/0/5	0	-	> 2000

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Female rats				
2000	0/0/5	0	-	> 2000

* Number of animals which died/number of animals with clinical signs/number of animals used
** ARY-0469-04/Atonik SL (Sodium 5-nitroguaiacolate 3 g/L. Sodium o-nitrophenolate 6 g/L. Sodium p-nitrophenolate 9 g/L); in GR registered (Reg. no: 8226 from 30.7.2014)

Table A 6: Summary of findings of acute dermal toxicity study in rats of ARY-0469-04 /Atonik SL

Mortality	No mortality occurred.
Clinical signs	No clinical signs of toxicity were observed.
Body weight	No adverse effect on body weight evolution.
Macroscopic examination	No clinical or macroscopic effect.

Conclusion
Under the experimental conditions. the dermal LD_{50} of ARY-0469-04/Atonik SL is higher than 2000 mg/kg bw in rats. Thus. no classification for acute dermal toxicity is required according to Regulation (EC) No. 1272/2008.

A 2.3.2 Study 2

Comments of zRMS:	Study *Acute dermal toxicity in xxxxxxs,* Xxxxxx S.R. 1985b has been previously evaluated and accepted at EU level in the DAR (2007) by RMS Greece. Because tested formulation has the same content of the active substance as in the formulation submitted for current zonal registration thus, outcome of the study can be considered as supportive for the ongoing registration assessment.

The following acute dermal toxicity studies with xxxxxxs were performed to provide guideline compliant data for the endpoint acute dermal toxicity in accordance with the requirements of Commission Regulation (EU) No 284/2013 and have been assessed and accepted at EU level for the inclusion of the Sodium nitrocompounds Na 5-NG, Na *o*-NP and Na *p*-NP in Annex I of Directive 91/414/EEC.

Reference	**KCP 7.1.2/02**
Report	xxxxxx 1985b. Acute dermal toxicity in xxxxxxs (Atonik) – HRC Report No 85434D/ ACM 12/AC
Guideline(s)	Yes/ US EPA Guideline 158.135 81-2. OECD guideline 402
Deviations	No control test was performed. but this study is acceptable.
Previous evaluation:	Yes, evaluated and accepted in the DAR (2007)
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-04/ Atonik SL (Lot: not reported.)
Species	Xxxxxx. Albino New Zealand White
No. of animals (group size)	5 males + 5 females
Dose(s)	2000 mg/kg bw
Exposure	24 hours (4 hours. semi-occlusive)

Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 7: Results of acute dermal toxicity study in xxxxxxs of ARY-0469-04 /Atonik SL**

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Male xxxxxxs				
2000	1/0/5	0	10 days	> 2000
Female xxxxxxs				
2000	0/0/5	0	-	> 2000

* Number of animals which died/number of animals with clinical signs/number of animals used
* *ARY-0469-04/Atonik SL (Sodium 5-nitroguaiacolate 3 g/L. Sodium o-nitrophenolate 6 g/L. Sodium p-nitrophenolate 9 g/L); in GR registered (Reg. no: 8226 from 30.7.2014)

Table A 8: Summary of findings of acute dermal toxicity study in xxxxxxs of ARY-0469-04 **/Atonik SL**

Mortality	One male was found dead on day 10; this death was not attributed to Atonik solution treatment.
Clinical signs	The dead animal was apparently normal until day 9 when nasal exudates. noisy respiration and general debility with the animal not eating or drinking was observed.
Body weight	A body weight loss was observed on day 8 for the dead xxxxxx.
Macroscopic examination	Severe congestion of the lungs. some purulent fluid in the lungs and heavy nasal exudates were observed in dead xxxxxx at the terminal necropsy.

Conclusion

Under the experimental conditions. the dermal LD_{50} of ARY-0469-04/Atonik SL is higher than 2000 mg/kg bw in xxxxxx. Thus, no classification for acute dermal toxicity is required according to Regulation (EC) No. 1272/2008.

A 2.3.3 Study 3

Comments of zRMS:	Study Xxxxxx(2009b) *Acute dermal toxicity* has been previously evaluated at EU level by zRMS Greece according to Uniform Principles. Study was accepted. Outcome of the study still is valid for the current registration. Under the experimental conditions, the dermal LD_{50} of ARY-0469-04 is higher than 2000mg/kg bw in rats. Thus, no classification for acute dermal toxicity is required according to Regulation (EC) No. 1272/2008.

The following study was performed to provide guideline compliant data for the endpoint acute oral toxicity in accordance with the requirements of Commission Regulation (EU) No 284/2013 and before the implementation of Regulation 1107/2009. This study has not been assessed at EU level.

Reference	**KCP 7.1.2/03**
Report	Xxxxxx(2009b) Acute dermal toxicity (limit test) with ATONIK PLUS (1.8). Unpublished report no.: 083570
Guideline(s)	Yes (OECD guideline 402)
Deviations	No
Previous evaluation:	No
GLP	Yes (certified laboratory)

Acceptability	Yes
Duplication (if vertebrate study)	Yes (The following study was performed before the implementation of the Regulation 1107/2009)

Study dates: 6 October 2008 to 27 January 2009

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-04/Atonik Plus (1.8%) (batch No. 040I8)
Species	Rats. Wistar
No. of animals (group size)	5 males + 5 females
Dose(s)	2000 mg/kg bw
Exposure	24 hours (skin, by a dressing throughout)
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 9: Results of acute dermal toxicity study in xxxxxxs of ARY-0469-04/Atonik Plus (1.8%)

Dose (mg/kg bw)	Toxicological results *	Duration of signs	Time of death	LD_{50} (mg/kg bw) (14 days)
Male rats				
2000	0/0/5	0	-	> 2000
Female rats				
2000	0/0/5	0	-	> 2000

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 10: Summary of findings of acute dermal toxicity study in xxxxxxs of ARY-0469-04/Atonik Plus (1.8%)

Mortality	No Mortality were observed
Clinical signs	No clinical signs, no skin reactions, were observed during the study
Body weight	The body weight gain of both males and females was not affected by treatment with the test substance.
Macroscopic examination	Macroscopic examination revealed no apparent abnormalities in all the animals

Conclusion

Under the experimental conditions, the dermal LD_{50} of ARY-0469-04/Atonik Plus (1.8%) is higher than 2000 mg/kg bw in rats. Thus, no classification for acute dermal toxicity is required according to Regulation (EC) No. 1272/2008.

A 2.4 Acute inhalation toxicity (KCP 7.1.3)

A 2.4.1 Study 1

Comments of zRMS:	Study is not accepted due to important limitation: - No information is provided concerning the content of the Atonik solution tested. - The nominal concentration of the test atmosphere was not reported.

The following study was performed to provide guideline compliant data for the endpoint acute inhalation toxicity in accordance with the requirements of Commission Regulation (EU) No 284/2013 and has been assessed and accepted at EU level for the inclusion of the Sodium nitrocompounds Na 5-NG, Na *o*-NP and Na *p*-NP in Annex I of Directive 91/414/EEC.

Reference	**KCP 7.1.3/01**
Report	Xxxxxx, 1990. Atonik solution: Acute Inhalation Toxicity Study in Rats 4 hour Exposure – HRC Report No. ACM14/85584
Guideline(s)	Yes / US EPA Guideline 152-12, 81-3.
Deviations	Yes / The purity of the test formulation was not reported. This deviation did not affect the quality or the integrity of the results obtained.
Previous evaluation:	Yes, evaluated and accepted in the DAR (2007)
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-04/Atonik SL (Lot: not reported.)
Species	Rat, Albino HC/CFHB (Wistar)
No. of animals (group size)	5 males + 5 females
Concentration(s)	6.7 mg/L air as aerosol
Exposure	4 hours
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 11: Concentration(s) and exposure conditions

Target conc. (mg/L air)	**Actual conc. (mg/L air)**	**MMAD * (µm)**	**GSD ** (µm)**
6.7	6.7	-	-

* 91% od 4-nitrophenol Na salt present associated with droplets of resporable size (<5.5 µm aerodynamic diameter)
** GSD = Geometric Standard Deviation

Table A 12: Results of acute inhalation toxicity study in rats of ARY-0469-04/Atonik SL

Concentration (mg/L air)	**Toxicological results**	**Duration of signs**	**Time of death**	**LC_{50} (mg/L air) (14 days)**
Male rats				
6.7	0/0/5	0	-	< 6.7
Female rats				
6.7	0/0/5	0	-	< 6.7

Table A 13: Summary of findings of acute inhalation toxicity study in rats of ARY-0469-04/Atonik SL

Mortality	No mortality occurred.

Clinical signs	Yes / Closing or partial closing of the eyes was observed in 4/5 males and 4/5 females during the 4-hour exposure period. An abnormal respiratory pattern was evident during exposure to Atonik solution in 3/5 males and 2/5 females. These signs were considered consistent with exposure to a moderately irritant aerosol. Yellow staining of the body fur was observed during both the exposure and observation periods in all rats exposed to Atonik solution
Body weight	The rats exposed to Atonik solution lost small amounts of weight (1 – 2 g) or had a reduced rate of bodyweight gain for 1 day following exposure and similar effects were observed in the control rats. Food and water consumption were unchanged following exposure to Atonik solution.
Macroscopic examination	There were no macroscopic or microscopic treatment-related findings detected. The ratio of lung weight to bodyweight ratio was considered to be within normal limits.

Conclusion
Under the experimental conditions, the inhalation LC_{50} of ARY-0469-04/Atonik SL is higher than 6.7 mg/L air in rats. Thus, no classification of acute inhalation toxicity is required according to Regulation (EC) No. 1272/2008.

A 2.4.2 Study 2

Comments of zRMS:	Study Xxxxxx (2009) *Acute inhalation toxicity* has been previously evaluated at EU level by zRMS Greece according to Uniform Principles. Study was accepted. Outcome of the study still is valid for the current registration. Under the experimental conditions the inhalation LC_{50} of ARY-0469-04 is higher than 5.02 mg/L air in rats. Thus, no classification of acute inhalation toxicity is required according to Regulation (EC) No. 1272/2008.

The following study was performed to provide guideline compliant data for the endpoint acute oral toxicity in accordance with the requirements of Commission Regulation (EU) No 284/2013 and before the implementation of Regulation 1107/2009. This study has not been assessed at EU level.

Reference	**KCP 7.1.3/02**
Report	Xxxxxx (2009) ATONIK PLUS (1.8%): Acute inhalation toxicity study in rats. Unpublished report no.: 26838
Guideline(s)	Yes (OECD 403)
Deviations	No
Previous evaluation:	No
GLP	Yes (certified laboratory)
Acceptability	Yes
Duplication (if vertebrate study)	Yes (The following study was performed before the implementation of the Regulation 1107/2009)

Study dates: 20 January 2009 to 3 February 2009

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-04/Atonik Plus (1.8%) (batch Nº 040I8)
Species	Rat. (Wistar)
No. of animals (group size)	5 males + 5 females
Concentration(s)	5.02 mg/L air as aerosol
Exposure	4 hours
Vehicle/Dilution	None

Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 14: Concentration(s) and exposure conditions

Target conc. (mg/L air)	Actual conc. (mg/L air)	MMAD * (µm)	GSD ** (µm)
5.02	5.02	2.15	1.97

* MMAD = Mass median aerodynamic diameter
** GSD = Geometric Standard Deviation

Table A 15: Results of acute inhalation toxicity study in rats of ARY-0469-04/Atonik Plus (1.8%)

Concentration (mg/L air)	Toxicological results*	Duration of signs	Time of death	LC_{50} (mg/L air) (14 days)
Male rats				
5.02	0/0/5	0	-	> 5.02
Female rats				
5.02	0/0/5	0	-	> 5.02

* Number of animals which died/number of animals with clinical signs/number of animals used

Table A 16: Summary of findings of acute inhalation toxicity study in rats of ARY-0469-04/Atonik Plus (1.8%)

Mortality	No mortality occurred.
Clinical signs	No clinical signs were observed.
Body weight	The body weight gain of both males and females was not affected by treatment with the test substance.
Macroscopic examination	Macroscopic examination revealed no apparent abnormalities in all the animals.

Conclusion

Under the experimental conditions. the inhalation LC_{50} of ARY-0469-04/Atonik Plus (1.8%) is higher than 5.02 mg/L air in rats. Thus, no classification of acute inhalation toxicity is required according to Regulation (EC) No. 1272/2008.

A 2.5 Skin irritation (KCP 7.1.4)

A 2.5.1 Study 1

Comments of zRMS:	Study Irritant effects on xxxxxx skin, Xxxxxx 1984a has been evaluated and accepted in the DAR 2007, however study is not valid for the current registration due to differences in composition between the reference formulation (ARY-0469-01) and the formulation submitted for registration ARY-0469-04

~~The following study was performed to provide guideline compliant data for the endpoint skin irritation in accordance with the requirements of Commission Regulation (EU) No 284/2013 and has been assessed and accepted at EU level for the inclusion of the Sodium nitrocompounds Na 5-NG, Na *o*-NP and Na *p*-NP in Annex I of Directive 91/414/EEC.~~

~~Reference~~	~~**KCP 7.1.4/01**~~
~~Report~~	~~Xxxxxx 1984a. Irritant effects on xxxxxx skin of Atonik solution – HRC Report No. 84642D/ACM7/SE~~

Guideline(s)	Yes / US EPA Guideline 158.135 81-5, OECD 404
Deviations	The batch No. and stability of the test substance were not reported. Nevertheless, this study was scientifically acceptable.
Previous evaluation:	Yes, evaluated and accepted in the DAR (2007)
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-04/Atonik SL (Lot: not reported.)
Species	Xxxxxx, New Zealand White
No. of animals (group size)	3 males
Initial test using one animal	No
Exposure	0.5 mL (4 hours, semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	4 days
Remarks	None

Results and discussions

Table A 17: Skin irritation of ARY-0469-04/Atonik SL

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		30 min	48 h	72 h	96 h		
1	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	-
2	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	-
3	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	-

Clinical signs:	No clinical signs of toxicity were observed.

Conclusion

Under the experimental conditions, ARY-0469-04/Atonik SL is not a skin irritant. Thus, no classification of skin irritation is required according to Regulation (EC) No. 1272/2008.

A 2.5.2 Study 2

Comments of zRMS:	Study Xxxxxx(2009c) *Acute dermal irritation/corrosion* has been previously evaluated at EU level by zRMS Greece according to Uniform Principles. Study was accepted. Outcome of the study still is valid for the current registration. Under experimental conditions product is no irritating for skin thus, no classification is required according to Regulation (EC) No. 1272/2008.

The following study was performed to provide guideline compliant data for the endpoint acute oral toxicity in accordance with the requirements of Commission Regulation (EU) No 284/2013 and before the implementation of Regulation 1107/2009. This study has not been assessed at EU level.

Reference	**KCP 7.1.4/02**
Report	Xxxxxx(2009c). Acute dermal irritation/corrosion with ATONIK PLUS (1.8%). Unpublished report no.: 090348
Guideline(s)	Yes (OECD 404)
Deviations	No
Previous evaluation:	No
GLP	Yes (certified laboratory)
Acceptability	Yes
Duplication (if vertebrate study)	Yes (The following study was performed before the implementation of the Regulation 1107/2009)

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-04/Atonik Plus (batch No. 040I8)
Species	Xxxxxx. New Zealand White
No. of animals (group size)	3 males
Initial test using one animal	No
Exposure	0.5 mL (4 hours. semi-occlusive)
Vehicle/Dilution	None
Post exposure observation period	3 days
Remarks	None

Results and discussions

Table A 18: Skin irritation of ARY-0469-04/Atonik Plus (1.8%)

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	-
2	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	-
3	Erythema Oedema	0 0	0 0	0 0	0 0	0 0	-

Clinical signs:	No clinical signs of toxicity were observed.

Conclusion

Under the experimental conditions. ARY-0469-04/Atonik Plus (1.8%) is not a skin irritant. Thus, no classification of skin irritation is required according to Regulation (EC) No. 1272/2008.

A 2.6 Eye irritation (KCP 7.1.5)

A 2.6.1 Study 1

Comments of zRMS:	Study *Irritant effects on the xxxxxx eye*, Xxxxxx 1984b has been evaluated and accepted in the DAR 2007, however study is not valid for the current registration due to differences in composition between the reference formulation (ARY-0469-01) and the formulation submitted for registration ARY-0469-04

~~The following study was performed to provide guideline compliant data for the endpoint eye irritation in accordance with the requirements of Commission Regulation (EU) No 284/2013 and has been assessed and accepted at EU level for the inclusion of the Sodium nitro compounds Na 5-NG, Na *o*-NP and Na *p*-NP in Annex I of Directive 91/414/EEC.~~

~~Reference~~	~~**KCP 7.1.5/01**~~
~~Report~~	~~Xxxxxx 1984b. Irritant effects on the xxxxxx eye of Atonik solution – HRC Report No. 84696D/ACM8/SE(G)~~
~~Guideline(s)~~	~~Yes / US EPA Guideline 158.135 81-4. OECD 405~~
~~Deviations~~	~~The batch No. and stability of the test substance were not reported. Nevertheless, this study was scientifically acceptable.~~
~~Previous evaluation:~~	~~Yes, evaluated and accepted in the DAR (2007)~~
~~GLP~~	~~Yes~~
~~Acceptability~~	~~Yes~~
~~Duplication (if vertebrate study)~~	~~No~~

~~Materials and methods~~

~~Test material (Lot/Batch No.)~~	~~ARY-0469-04/Atonik SL (Lot: not reported.)~~
~~Species~~	~~Xxxxxx. New Zealand White~~
~~No. of animals (group size)~~	~~2 males + 1 female~~
~~Initial test using one animal~~	~~No~~
~~Exposure~~	~~e.g. 0.1 mL (single instillation in conjunctival sac)~~
~~Irrigation (time point)~~	~~After administration the eye lids were gently held together for about one second in order to limit loss of the material.~~
~~Vehicle/Dilution~~	~~None~~
~~Post exposure observation period~~	~~e.g. 14 days~~
~~Remarks~~	~~e.g. None~~

~~Results and discussions~~

~~Table A 19: Eye irritation of ARY-0469-04/Atonik SL~~

~~Animal No.~~		~~Scores after treatment *~~				~~Mean scores (24-72 h)~~	~~Reversible (day)~~
		~~1 h~~	~~24 h~~	~~48 h~~	~~72 h~~		
~~1~~	~~Corneal opacity~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~-~~
	~~Iritis~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	
	~~Redness conjunctivae~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	
	~~Chemosis conjunctivae~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	
~~2~~	~~Corneal opacity~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	~~-~~
	~~Iritis~~	~~0~~	~~0~~	~~0~~	~~0~~	~~0~~	

	~~Redness conjunctivae~~ ~~Chemosis conjunctivae~~	~~0~~ ~~0~~	~~0~~ ~~0~~	~~0~~ ~~0~~	~~0~~ ~~0~~	~~0~~ ~~0~~	
~~3~~	~~Corneal opacity~~ ~~Iritis~~ ~~Redness conjunctivae~~ ~~Chemosis conjunctivae~~	~~0~~ ~~0~~ ~~0~~ ~~0~~	~~0~~ ~~0~~ ~~0~~ ~~0~~	~~0~~ ~~0~~ ~~0~~ ~~0~~	~~0~~ ~~0~~ ~~0~~ ~~0~~	~~0~~ ~~0~~ ~~0~~ ~~0~~	~~-~~

~~**Clinical signs:**~~	~~No clinical signs of toxicity were observed. (If yes, describe kind of signs)~~

~~**Conclusion**~~
~~Under the experimental conditions, ARY-0469-04/Atonik SL is not an eye irritant. Thus, no classification as an eye irritant is required according to Regulation (EC) No. 1272/2008.~~

A 2.6.2 Study 2

Comments of zRMS:	Study Xxxxxx(2009d) *Acute eye irritation/corrosion* has been previously evaluated at EU level by zRMS Greece according to Uniform Principles. Study was accepted. Outcome of the study still is valid for the current registration. Under experimental conditions only slight irritation was observed after instillation of tested material into the conjunctival sac of xxxxxxs (animals 1 and 2 showed redness grade 1 of the conjunctivae 1 h post exposition). Product is no irritating for eyes thus, no classification is required according to Regulation (EC) No. 1272/2008.

The following study was performed to provide guideline compliant data for the endpoint acute oral toxicity in accordance with the requirements of Commission Regulation (EU) No 284/2013 and before the implementation of Regulation 1107/2009. This study has not been assessed at EU level.

Reference	**KCP 7.1.5/02**
Report	Xxxxxx(2009d) Acute eye irritation/corrosion with ATONIK PLUS(1.8%). Document nº: 083573
Guideline(s)	Yes (OECD 405)
Deviations	No
Previous evaluation:	No
GLP	Yes (certified laboratory)
Acceptability	Yes
Duplication (if vertebrate study)	Yes (The following study was performed before the implementation of the Regulation 1107/2009)

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-04/Atonik Plus (1.8%) (batch no. 040I8.)
Species	Xxxxxx. New Zealand White
No. of animals (group size)	3 female
Initial test using one animal	No
Exposure	0.1 mL (single instillation in conjunctival sac)
Irrigation (time point)	After administration the eye lids were gently held together for about one second in order to limit loss of the material.
Vehicle/Dilution	None
Post exposure observation period	14 days
Remarks	None

Results and discussions

Table A 20: Eye irritation of ARY-0469-04/Atonik Plus (1.8%)

Animal No.		Scores after treatment *				Mean scores (24-72 h)	Reversible (day)
		1 h	24 h	48 h	72 h		
1	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	
	Redness conjunctivae	1	0	0	0	0	
	Chemosis conjunctivae	0	0	0	0	0	
2	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	
	Redness conjunctivae	1	0	0	0	0	
	Chemosis conjunctivae	0	0	0	0	0	
3	Corneal opacity	0	0	0	0	0	-
	Iritis	0	0	0	0	0	
	Redness conjunctivae	0	0	0	0	0	
	Chemosis conjunctivae	0	0	0	0	0	

Clinical signs:	Animals 1 and 2 showed redness grade 1 of the conjunctivae 1 h post instillation. No further signs of irritation were observed 24 hours post instillation.

Conclusion

Under the experimental conditions. ARY-0469-04/Atonik Plus (1.8%) is not an eye irritant. Thus, no classification as an eye irritant is required according to Regulation (EC) No. 1272/2008.

A 2.7 Skin sensitisation (KCP 7.1.6)

Comments of zRMS:	Study Xxxxxx(2010) *Test for sensitisation (local lymph node assay – LLNA)* has been previously evaluated at EU level by zRMS Greece according to Uniform Principles. Study was accepted. Outcome of the study still is valid for the current registration. Under the experimental conditions tested material is not a skin sensitizer. Thus, no classification as a skin sensitizer is required according to Regulation (EC) No. 1272/2008.

A 2.7.1 Study 1

The following study with guinea pigs was performed to provide guideline compliant data for the endpoint skin sensitisation in accordance with the requirements of Commission Regulation (EU) No 284/2013 and before the implementation of the Regulation 1107/2009. This study has not been assessed at EU level.

Reference	**KCP 7.1.6/01**
Report	Xxxxxx. A. 2010. Test for sensitisation (local lymph node assay – LLNA) with ATONIK PLUS (1.8%) BSL BIOSERVICE Scientific Latoratories GmbH, Germany Report no. 083574
Guideline(s)	Yes (OECD 429. EPA 712-C-03-197)
Deviations	No deviation from project protocol.
Previous evaluation:	No
GLP	Yes (certified laboratory)
Acceptability	Yes
Duplication (if vertebrate study)	Yes (The following study was performed before the implementation of the Regulation 1107/2009)

Materials and methods

Test material (Lot/Batch No.)	ARY-0469-01/ Atonik SL / Atonik Plus (batch No. 040I8)
Species	Mice. female. CBA / Ca0laHsd
No. of animals (group size)	Preliminary: 4 (3+1) Main study: 20 (3x5+1x5)
Range finding	Preliminary: Highest tolerated non-irritant test: 3 animals. topical. ear: 100%. 50%. 25% + 1 animal . topical. ear: 100% AOO.
Exposure (concentration(s). no. of applications)	Main study: Test substance. 3 groups: topical. ear: 100%. 50%. 25% Negative control: 1 goup. topical. ear:: 100% AOO
Vehicle	AOO (3+1 (v/v) Acetone/olive oil)
Pretreatment prior to topical application	No
Reliability check	Yes. P-phenylenediamnine positive control. QA-audited. archived (BSL ID 0835321)
Remarks	None

Results and discussions

Table A 21: Radioactive determination of ARY-0469-04/Atonik Plus (1.8%)

Group	Animal	DPM	DPM (corrected against background)	DPM/node	Stimulation index
Negative control	16	769	745.6	372.8	
	17	1318.0	1294.6	647.3	
	18	991.0	967.6	483.8	
	19	1377.0	1353.6	676.8	
	20	863.0	839.6	419.8	
	MV ± SD	**1063.6 ± 243.0**	**1040.2 ± 243.0**	**520.1 ± 121.5**	**1.0**
25% ATONIK PLUS (1.8%)	1	1856.0	1832.6	916.3	1.8
	2	692.0	668.6	334.3	0.6
	3	1170.0	1146.6	573.3	1.1
	4	1004.0	980.6	490.3	0.9
	5	665.0	641.6	320.8	0.6
	MV ± SD	**1077.4 ± 433.3**	**1054.0 ± 433.3**	**547.0 ± 216.7**	**1.0 ± 0.4**
50% ATONIK PLUS (1.8%)	6	569.0	545.6	272.8	0.5
	7	907.0	883.6	441.8	0.8
	8	994.0	970.6	485.3	0.9
	9	234.0	210.6	105.3	0.2
	10	916.0	892.6	446.3	0.9
	MV ± SD	**724.0 ± 285.4**	**700.6 ± 285.4**	**350.3 ± 142.7**	**0.7 ± 0.3**
100% ATONIK PLUS (1.8%)	6	699.0	675.6	337.8	0.6
	7	663.0	639.6	319.8	0.6
	8	1262.0	1238.6	619.3	1.2
	9	534.0	510.6	255.3	0.5
	10	554.0	530.6	265.3	0.5
	MV ± SD	**724.0 ±267.2**	**719.0 ± 267.2**	**359.5 ± 133.6**	**0.7 ± 0.3**
		Background	**23.4 ± 3.7**		

Table A 22: Summary of skin sensitisation study of Atonik Plus (1.8%) -LLNA Sensitisation Index

Test Item Concentration	Stimulation Index (Mean value ± standard deviation)	Lymph Node Weights (mg)
25%	1.0 ± 0.4	3.0
50%	0.7 ± 0.3	2.5
100%	0.7 ± 0.3	2.4
Vechile (AOO)	1.0 ± 0.0	2.6
Positive Control (PD)	10.9 ± 1.7	-

AOO = 3/1 (v/v) Acetone/Olive Oil; PD = Phenylene-Diamine

None of the 3 tested concentrations of the test item reached the stimulation index (EI) of 3 (see Table A22) Results of radioactivity determination were supported by the means of the lymph node weights per group, which showed no significant difference compared to the negative control.

Clinical signs:	Body weight: All animals showed the expected weight development, which include a weight loss of up to 2 g throughout the study. Weight of lymph nodes: The means of lymph node weights per group showed no significant difference compared to the negative control.

Conclusion

The overall conclusion of this study was that the results of radioactivity measures were supported by mean

lymph node weights per group, and that there was no evidence to suggest that Atonik Plus presents and sensitising potential, and therefore it should not be regarded as a dermal sensitiser.

Under the experimental conditions. ARY-0469-04/Atonik Plus (1.88%) is not a skin sensitizer. Thus, no classification as a skin sensitizer is required according to Regulation (EC) No. 1272/2008.

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

There are no supplementary studies available for combination of plant protection products.

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)

An *in vitro* dermal absorption study was performed on sodium *p*-nitrophenolate (Na *p*-NP) and was submitted in support of the dermal absorption assessment. The study was not assessed during the EU review. Therefore a summary of this study has been provided.

Comments of zRMS:	Study I*n vitro dermal absorption study*, Craig. S. (2012) performed on sodium p-nitrophenolate (Na p-NP) has been previously evaluated at EU level by zRMS Greece according to Uniform Principles. Study was accepted. The dermal absorption value derived for the Na p-NP was considered applicable for the other two a.i. considering that all three substances are of similar toxicokinetics profile. Outcome of the study still is valid for the current registration. Dermal absorption value of 8% proposed for the concentrate and 27% for dilute of sodium-p nitrophenolate has been accepted by the zRMS PL

Reference	KCP 7.3.1
Report	Craig. S. (2012). Sodium *p*-nitrophenolate: The *in vitro* percutaneous absorption of radiolabelled pesticide in the concentrate and a single in-use spray dilution through human skin. Doc. No. 791509
Guideline(s)	OECD No. 428 (2004). OECD No. 28 (2004). SANCO/222/2000/Rev. 7 (2004)
Deviations	None
GLP	Yes
Acceptability	Yes
Duplication (if vertebrate study)	No

Materials and methods

Test material	Name (Lot/Batch No.)	Sodium *p*-nitrophenolate (purity 100.7%. batch no.: 353L1)
	Test preparation	radioformulation
	Specific activity	54 mCi/mmol
	Radiochemical purity	99.2%
Product	Name (Lot/Batch No.)	([14C]-sodium p-nitrophenolate and unlabelled samples of the

		other active substances (sodium o nitrophenolate and sodium 5 nitroguaiacolate) were added to the formulation preparations in the correct proportions to mimic the final ATONIK formulation.
	Company code	ARY-0469-01
	Concentration a.s.	sodium 5-nitroguaiacolate: 1 g/L sodium *o*-nitrophenolate: 2 g/L sodium *p*-nitrophenolate: 3 g/L
	Formulation type	SL

Test system		
Diffusion cell	Cell type	static
	(if dynamic) Flow rate	-
	Exposed skin area	3.14 cm²
	Cover	-
Membrane	Skin type	dermatomed
	Skin thickness range	Split thickeness = 380-400 µm
	Skin donors age	25-56 years (4 donors)
	Skin donors sex	1M + 3F
	Location	3 abdominal and 1 breast
	Source	ex vivo
	Integrity test	Yes
Receptor	Receptor medium	receptor fluid. a tissue culture medium containing polyoxyethylene 20 oleyl ether (6 %. w/v). glucose (1 %. w/v). sodium azide (0.01 %. w/v) streptomycin (0.1 mg/mL) and penicillin G (100 units/mL)
	Solubility in receptor medium	9.42. receptor fluid is not rate limiting for solubility
Sample Time	Exposure time	8 hours
	Observation time	16 h
Sampling	Sample intervals	0.5 . 1. 2. 4. 8 and 24 hours
Washing		post exposure
Final Procedure	Tape stripping	y
	TS1-2 analysed separately	n
Remarks:		

Summary
Atonik (SL formulation) contains 3 active components; Sodium 5-nitroguaiacolate (Na 5-NG), Sodium *o*-nitrophenolate (Na *o*-NP) and Sodium *p*-nitrophenolate (Na *p*-NP) at 1, 2 and 3 g/L, respectively.
The dermal absorption of Sodium *p*-nitrophenolate was assessed in this study. The in-use spray dilution is produced by mixing 1 L of formulation with 2000 L of water to generate a final Sodium *p*-nitrophenolate concentration of *ca* 0.0015 g/L.
The study was conducted according to the OECD principles of Good Laboratory Practice and was performed following SANCO/222/2000/Rev.7 and OECD Guideline for Testing of Chemicals (Guideline 428) and OECD Guidance Document No. 28.
The skin samples were 4 (3 abdomen and 1 chest) and were obtained from 4 donors of age between 2 and 56 years. These samples came from the NHS Lothian, St. John's Hospital, Livingston, UK. They were removed using a Zimmer ® electric dermatome with a final thickness of 200-400 µm. The integrity of the membranes was measured by electrical resistance. Split-thickness human skin membranes were mounted into static diffusion cells containing receptor fluid, a tissue culture medium containing polyoxyethylene 20 oleyl ether (6 %, w/v), glucose (1 %, w/v), sodium azide (0.01 %, w/v) streptomycin (0.1 mg/mL) and penicillin G (100 units/mL), in the receptor chamber. The skin surface temperature was maintained at 32 °C ± 1°C throughout the experiment. An electrical resistance barrier integrity test was performed for split-thickness skin and any sample exhibiting a resistance <4 kilo ohms (kΩ) was excluded from subsequent absorption measurements.
The formulation concentrate and in-use spray dilution were prepared containing Sodium *p*-nitrophenolate at 3 g/L and 0.0015 g/L, respectively. The test preparations were applied at an application volume of 10 µL/cm2 to human split-thickness skin membranes mounted into static diffusion cells *in vitro*.
Percutaneous absorption was assessed by manually collecting receptor fluid fractions at 0.5, 1, 2, 4, 8 and 24 h post-application. At 8 h post application, exposure was terminated by washing the skin surface with a

concentrated commercial hand wash soap followed by rinsing with a dilute soap solution and drying the skin surface with tissue paper (tissue swabs). At 24 h post application (*i.e.* after a 16 h post exposure monitoring period), the skin sample was removed from the static diffusion cells and dried. The receptor fluid in the receptor chamber was removed and retained in a bulk receptor fluid vial. The *stratum corneum* was removed with 20 successive tape strips. The remaining skin was divided into exposed and unexposed skin and solubilised with tissue solubiliser. All samples were analysed by liquid scintillation counting.

Table A 3: Summary of the mean results following topical application of [14C]- sodium p-nitrophenolate to dermatomed human skin 24 h post dose

Test preparation (No.)	**Concentrate (1)**		**In-Use Dilution (2)**	
Target [Sodium p-nitrophenolate] in Test preparation	3.00 mg/mL		0.0015 mg/mL	
Actual [Sodium p-nitrophenolate] in Test preparation by radioactivity	3.19 mg/mL		0.00139 mg/mL	
Application Rate of Test preparation	10 µL/cm²		10 µL/cm²	
Application Rate of Sodium p-nitrophenolate	31.87 µg equiv/cm²		13.92 ng equiv/cm²	
Distribution	(% Applied Dose)	(µg equiv./cm²)	(% Applied Dose)	(µg equiv./cm²)
Dislodgeable Dose (8 h)	92.93	29.61	71.62	9.97
Total Dislodgeable Dose (24 h)	93.02	29.63	72.37	10.07
Unabsorbed Dose	93.78	29.87	75.75	10.55
Total Absorbed Dose	3.92	1.25	19.40	2.70
Dermal Delivery	4.84	1.54	22.85	3.18
Potentially Absorbable Dose	5.39	1.72	25.55	3.56
Mass Balance	98.62	31.42	98.61	13.73

Dislodgeable dose (8 h) = skin wash (8 h) + tissue swab (8 h) + pipette tip (8 h)
Total unabsorbed dose = dislodgeable dose (8 h) + tissue swab (24 h) + donor wash + tape strips 1-20 +unexposed skin
Total Absorbed dose = cumulative receptor fluid + receptor wash. Dermal delivery = exposed skin + total absorbed dose
Potentially absorbable dose = dermal delivery + tape strips 3-20. Mass balance = unabsorbed dose + dermal delivery

Results and discussions

The study was carried out with a soluble concentrate (SL) of sodium p-nitrophenolate. The dose those used were 3 g a.i./1, which correspond to the concentrated formulation, and 0.0015 g a.i./1, representative of the application dilution. The exposure time was 8 hours. After that time, the skin was washed with a detergent solution. The total time of observation was 24 hours.
For the concentrated dose the cells were numbered from 10 to 18 and for the diluted dose from l to 9.
Recipient fluid samples were collected at 0.5, 1, 2, 4, 8, and 24 hours post dosage:

Table 16 Cumulative Absorption (% Applied Dose) of [14C]-Sodium p-nitrophenolate into Receptor Fluid Following Topical Application of [14C]-Sodium p-nitrophenolate in Test Preparation 1 (3 g/L) to Human Split-Thickness Skin

	Cell Number and Donor Number										
	Cell 10	Cell 11	Cell 12	*Cell 13*	Cell 14	Cell 15	Cell 16	Cell 17	Cell 18		
Time (h)	0339	0339	0318	*0318*	0322	0322	0322	0337	0337	Mean	SD
0	0.00	0.00	0.00	*0.00*	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.16	0.17	*0.04	*0.05*	*0.03	*0.02	*0.02	*0.04	*0.01	°0.06	°0.06
1	1.26	1.51	0.36	*0.71*	0.25	0.05	0.14	0.23	0.09	0.49	0.57
2	2.81	3.50	1.04	*2.63*	0.78	0.13	0.54	0.79	0.43	1.25	1.22
4	4.05	5.08	1.72	*5.93*	1.58	0.24	1.16	1.29	0.82	1.99	1.68
8	5.06	6.07	1.88	*7.85*	1.93	0.32	1.25	1.72	1.23	2.43	2.02
24	5.52	6.57	2.34	*11.45*	2.68	0.54	1.62	1.97	1.61	2.86	2.08

Cell 13 rejected as an outlier for total absorbed (total absorbed greater than mean + 2SD)
*=Results calculated from data less than 30 d.p.m. above background
°=Mean and SD includes results calculated from data less than 30 d.p.m above background

Remarks

Absorption profile for Cell 13 increased at a higher rate than the other samples. Although the value of Cell 13 could be rejected as an outlier for clear statistical criteria (total absorbed greater than mean + 2SD), the study does not plausible cause for this cell was an outlier. Thus, it should be considered part of normal experimental variation and not be left out. Hence the results are provided as mean values (n = 9).

Table 17 Cumulative Absorption (% Applied Dose) of [14C]-Sodium p-nitrophenolate into Receptor Fluid Following Topical Application of [14C]-Sodium p-nitrophenolate in Test Preparation 2 (0.00015 g/L) to Human Split-Thickness Skin

	Cell Number and Donor Number										
Time (h)	Cell 1 0339	Cell 2 0339	Cell 3 0318	Cell 4 0318	Cell 5 0318	Cell 6 0322	Cell 7 0322	Cell 8 0337	Cell 9 0337	Mean	SD
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	*0.68	*0.86	*0.71	*0.29	*0.55	*0.12	*0.14	*0.32	*0.45	°0.46	°0.26
1	*2.78	5.71	*2.02	*1.00	*0.80	*0.23	*0.74	*0.72	*0.47	°1.61	°1.74
2	10.53	14.38	7.35	*2.78	4.79	*1.70	*2.59	*0.63	*0.95	°5.08	°4.76
4	16.60	19.88	13.70	7.67	9.58	6.68	6.01	*2.02	*2.21	°9.37	°6.21
8	19.35	22.98	17.96	10.75	16.17	11.75	12.51	4.47	4.00	13.33	6.46
24	21.56	24.70	24.62	15.87	20.51	19.26	16.18	13.79	10.74	18.58	4.80

*=Results calculated from data less than 30 d.p.m. above background
°=Mean and SD includes results calculated from data less than 30 d.p.m above background

Remarks

Similar absorption profiles were observed for all samples. The results are provided as mean values (n = 9).

At the end of the experiment, the stratum corneum was extracted with the application of 20 adhesive strips on the treated skin, discarding the first two strips.

The study shows recovery data at the middle of the study (12 h) through plots of absorption exposure versus time (Figure 1 and Figure 2).

Figure 1 Graph of absorption of p-nitrophenolate vs. time both in human skin at the concentrated dose (3g/1)

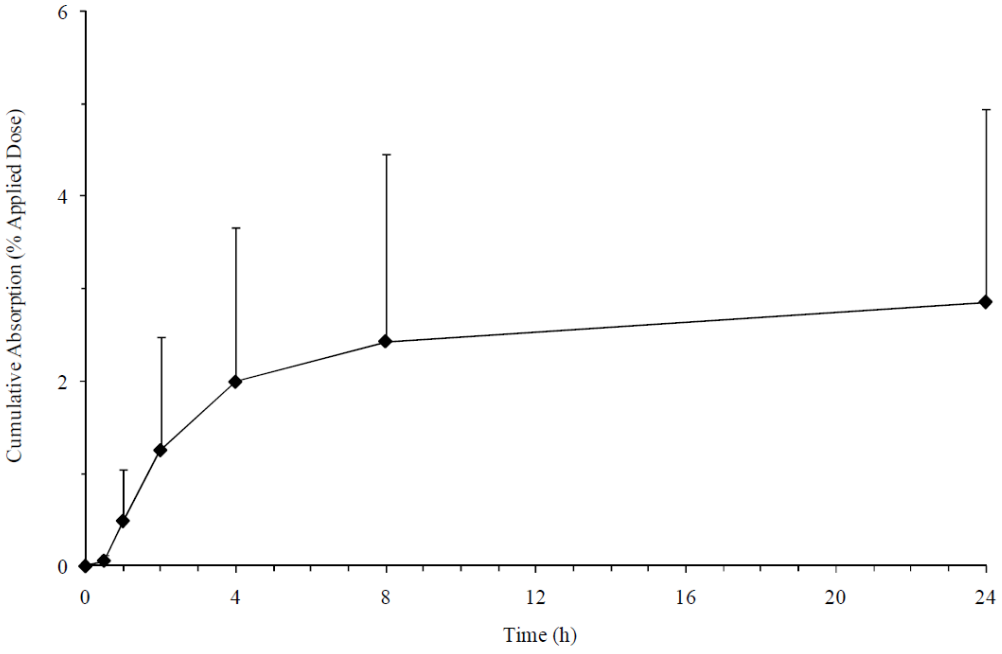
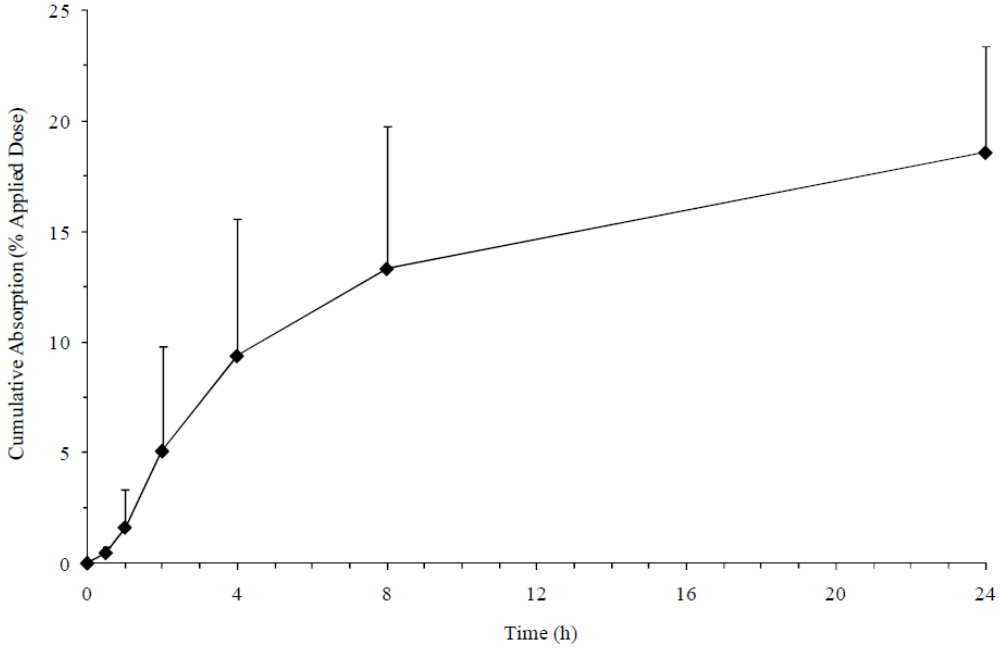


Figure 2 Graph of absorption of p-nitrophenolate vs. time both in human skin at the diluted (0.0015 g/1).



As shown in both graphs, during the first half of the study (12 hours), absorbed more than 75% of the total absorbed at the end of it at both doses (for the concentrated and diluted dose respectively), therefore, it will not be taken into account for the final absorption of the percentage of p-nitrophenolate retained in the stratum corne≤um.

Therefore, is considered as absorbed material, the amount of active substance retained in the receptor fluid, in the receptor chamber wash and on the skin after washing excluding the stratum corneum.

Below are the absorption data for the two doses at the end of the study (8 hours of exposure and 24 hours of observation)

Table 18 Summary of the results from the individual cells and mean results of the concentrate formulation (3 g/l)

	Results (%) from individual cells									**mean**	**SD**
	Cell 10	Cell 11	Cell 12	Cell 13	Cell 14	Cell 15	Cell 16	Cell 17	Cell 18		
Exposed skin	1,11	1,3	0,65	2,4	1,02	0,71	0,49	0,4	0,24	0,92	0,65
Receptor fluid	5,52	6,57	2,34	11,45	2,68	0,54	1,62	1,97	1,61	3,81	3,47
Receptor Chamber wash	0,19	0,19	0,05	0,21	0,1	0,02	0,05	0,07	0,06	0,10	0,07
Stratum corneum (1-20)	1,190	0,950	1,010	1,100	0,550	0,230	0,470	0,510	0,580	0,73	0,33
Dermal absrorption	6,820	8,060	3,040	14,060	3,800	1,270	2,160	2,440	1,910	4,840	4,152
RECOVERY	**98,98**	**97,85**	**98,02**	**98,74**	**98,18**	**100,1**	**98,8**	**99,31**	**97,6**	**98,62**	**0,79**
Dermal absorption: %exposed skin + % in receptor fluid + %receptor chamber wash											
Cell 13 = although this value could be rejected as an otlier for clear statistical criteria (total absorbed greater than mean + 2SD), the study does not pausible cause for this cell was outlier. Thus, it should be considered part of normal experimental variation and not be left out.											
Thus, to address **variability between replicates/animals, dermal absorption should be calculated as** follows: Absorption (mean value) + ks, where s is the sample standard deviation.								**Absorption Mean**		**4,84**	**4,15**
								Nº of replicates (n)		9,0	
								Multiplication factor (k)		0,77	
								Dermal Abs. of concentrat		**8,04 %**	

The recovery values were within the levels recommended in the dermal absorption EFSA 2017 guide >95% (98.62 for concentrate dose)
According the EFSA Guidance Document on Dermal Absorption (EFSA Journal 2017;15(6):4873), the preferred approach to addressing variability between replicates is to add a multiple of the standard deviation to the mean value. The multiplication factor required depends on the number of replicates, in this study n = 9 and the multiplication factor, k = 0.77.

Thus, to address variability between replicates, dermal absorption should be calculated as follows: Absorption (mean value) + ks, where s is the standard deviation.

Absorption dermal of dilute = 4.84 + 0.77 x 4.15 = 8.04 %

Table 19 Summary of the results from the individual cells and mean results of the concentrate formulation (3 g/l)

	Results (%) from individual cells									mean	SD
	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6	Cell 7	Cell 8	Cell 9		
Exposed skin	3,37	3,08	4,2	3,49	4,47	3,47	2,99	3,96	2,1	3,46	0,71
Receptor fluid	21,56	24,7	24,62	15,87	20,51	19,26	16,18	13,79	10,74	18,58	4,80
Receptor Chamber wash	1,01	1,1	0,85	0,78	0,77	1,06	0,73	0,62	0,41	0,81	0,22
Stratum corneum (1-20)	1,29	2,43	3,25	3,73	4,32	2,70	2,54	6,30	2,84	3,27	1,42
Dermal absrorption	25,94	28,88	29,67	20,14	25,75	23,79	19,90	18,37	13,25	22,85	5,36
RECOVERY	**98,72**	**97,86**	**99,23**	**97,95**	**98,68**	**99,31**	**98,24**	**98,12**	**99,36**	**98,61**	**0,59**
Dermal absorption: %exposed skin + % in receptor fluid + %receptor chamber wash											
Thus, to address **variability between replicates/animals, dermal absorption should be calculated**								**Absorption Mean**		**22,85**	**5,36**
as follows: Absorption (mean value) + ks, where s is the sample standard deviation.								Nº of replicates (n)		9,0	
								Multiplication factor (k)		0,77	
								Dermal Abs. of diluted		**27,0 %**	

The recovery values were within the levels recommended in the dermal absorption EFSA 2017 guide >95% (98.61% for the diluted dose)
According the EFSA Guidance Document on Dermal Absorption (EFSA Journal 2017;15(6):4873), the preferred approach to addressing variability between replicates is to add a multiple of the standard deviation to the mean value. The multiplication factor required depends on the number of replicates, in this study n = 9 and the multiplication factor, k = 0.77.

Thus, to address variability between replicates, dermal absorption should be calculated as follows: Absorption (mean value) + ks, where s is the standard deviation.

Absorption dermal of dilute = 22.85 + 0.77 x 5.36 = 27 %

Conclusion/endpoint:
According the EFSA Guidance Document on Dermal Absorption (EFSA Journal 2017;15(6):4873), for the concentrate formulation tested on human skin, it is considered appropriate uses the dermal absorbed dose, being the result 8.04%, and the final dermal absorption values should be rounded to 8.0%.
According the EFSA Guidance Document on Dermal Absorption (EFSA Journal 2017;15(6):4873), for the dilute formulation tested on human skin, it is considered appropriate uses the dermal absorbed dose, being the result 27.0%, and the final dermal absorption values should be rounded to 27%.

As result, a dermal absorption value of 8% is proposed for the concentrate and 27% for dilute of sodium-p nitrophenolate in Atonik.
The dermal absorption value derived for the Na *p*-NP is considered applicable for the other two a.i. (Na 5-NG and Na *o*-NP) considering that all three substances are of similar toxicokinetics profile.

A 2.11 Other/Special Studies

No other studies submitted.

Appendix 3 Exposure calculations

A 3.1 Operator-Worker-Bystander and Resident exposure calculations (KCP 7.2.1.1, KCP 7.2.3.1 and KCP 7.2.2.1)

Summary table of operator-worker and bystander -resident exposure

		Model
Calculations of Operator, Worker and Bystander - Resident according EFSA guidance		
Table A1	Sodium 5-Nitroguaicolate on Oilseed rape, low crops-vehicle mounted	 A1.EFSA model 5-nitro OILSEED-trac
Table A2	Sodium o-Nitrophenolate on Oilseed rape, low crops-vehicle mounted	 A2.EFSA model O-nitro OILSEED-tra
Table A3	Sodium p-Nitrophenolate on Oilseed rape, low crops-vehicle mounted	 A3.EFSA model P-nitro-OILSEED-trac
Calculations of Worker according EUROPOEM II		
Table A4	Sodium 5-Nitroguaicolate on Oilseed rape, worker exposure	 A4.Worker-Europoe m-ii-5-nitro.xls
Table A5	Sodium o-Nitrophenolate on Oilseed rape, worker exposure	 A5.Worker-Europoe m-ii-0-nitro.xls
Table A6	Sodium p-Nitrophenolate on Oilseed rape, worker exposure	 A6.Worker-Europoe m-ii-p-nitro.xls

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)

No studies reported.