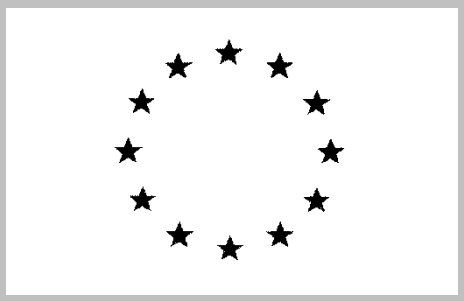
European Commission



Renewal Assessment Report
prepared according to Regulation (EC) N° 1107/2009

Aluminium silicate calcined (Kaolin Calcined)

Volume 3 – B.6 (AS)

Rapporteur Member State: Greece
Co-Rapporteur Member State: France

May 2020

Version History

Date	Data points containing amendments or additions and brief description
March 2008	Draft Assessment Report (DAR) – prepared by RMS Hungary in the context of the application for the first inclusion of the a.s. aluminium silicate in Annex I to Council Directive 91/414/EEC.
May 2011	Final Addendum to the DAR
May 2020	Draft Renewal Assessment Report (RAR) – prepared by RMS EL in the context of the application for renewal of approval of the a.s. according to Reg (EU) No 1107/2009. *NOTE: The RAR is a stand-alone document containing the evaluations already displayed in the initial DAR, as well as the new assessments. The revision of the initial DAR has been done in accordance with SANCO/10180/2013 rev.1 (March 2013), with changes in the original text – resulting from assessment of new studies (or reconsideration of old studies or studies that were not yet previously peer-reviewed) – being highlighted by means of yellow shading.*

Table of Contents

B.6 TOXICOLOGY AND METABOLISM

General comment	The RAR includes re-evaluations of existing data previously displayed in the DAR (2008), as well as new assessments considering the limited data/information submitted in the context of the renewal of the active substance (a.s.) aluminium silicate calcined (Kaolin calcined). All additions/corrections to the DAR are highlighted in yellow colour. Two dossiers have been submitted for the purpose of the a.s. renewal, one by the Tessenderlo Group N.V. and one by the notifier SOKA. Tessenderlo Chemie N.V. had supported the original Annex I inclusion of aluminium silicate. Information regarding the systematic literature search performed by Tessenderlo Group N.V. and by SOKA are presented in APPENDICES III and IV, respectively.

INTRODUCTION

- **EU Regulatory history for use in Plant Protection Products**

Aluminum silicate (aka kaolin) was included in Annex I to Council Directive 91/414/EEC by Commission Directive 2008/127/EC. Since the replacement of Directive 91/414/EEC by Regulation (EC) No 1107/2009, Aluminum silicate (aka kaolin) is approved under Commission Implementing Regulation 2017/195 amending Commission Implementing Regulation (EU) No 540/2011 as regards the extension of the approval periods of several active substances listed in Part B of the Annex to Implementing Regulation (EU) No 686/2012 (AIR IV renewal programme).

Following the EFSA peer review no ADI or ARfD were established because consumer exposure was considered to be very unlikely. However, regarding operator exposure, the use of an inhalation exposure limit (IEL) of 36.6 mg/day, derived from the workplace exposure limit time weighted average (WEL-TWA) of 2 mg/m, was considered adequate in the absence of an AOEL and conservative for an agricultural setting. Assessment of the inhalation operator exposure led to different outcomes (above/below WEL-TWA) dependent on the model used. Thus, as stated in the Review Report SANCO/2603/08 (rev.2, 01 June 2012) for the inclusion of aluminium silicate in Annex I of Directive 91/414/EEC, risk mitigation measures were recommended, i.e. *the conditions of use shall include the application of adequate personal and respiratory protective equipment, where appropriate*.

Regarding the impurity profile of the a.s., a maximum level of 0.1% was set for the impurity crystalline silica, considered to be of toxicological concern on the basis of the available information. However, based on the minimum purity of 999.8 g/kg specified by the main data submitter at that time, the limit for the total impurity content was 0.02% maximum i.e. more restrictive.

In the frames of the renewal of the a.s. the minimum purity specified is 999 g/kg, while crystalline silica with diameter below 10 μm is defined as relevant impurity with a maximum limit of 1 g/kg.

This is in line with the conclusion drawn for the a.s. keiselgur (diatomaceous earth) [EFSA Conclusion on the Peer review of the pesticide risk assessment of the active substance kieselgur (diatomaceous earth), 2020]. Crystalline silica (CAS 14808-60-7) is a substance not included in Annex VI of Regulation 1272/2008 (CLP). However, according to the International Agency for Research of Cancer (IARC), crystalline silica dust causes cancer of the lung. IARC category 1 assigned for crystalline silica is equivalent to Carc 1A; H350i according to CLP Regulation for which the generic concentration limit triggering classification is 0.1%.

It is noted that the proposal to change the restriction previously set for the particle size diameter from of 50 μm to 10 μm was drawn following the discussion in the Pesticide Peer Review Meeting 18 (04-08 November 2019), where the following have been concluded: As “Respirable dust” generally refers

to particles small enough to reach the alveolar spaces in the lung (i.e., ≤ 10 µm in aerodynamic diameter) and comprises particles sufficiently small to reach the deep lung. Respirable fraction is defined according to EN 481 (Workplace atmospheres. Size fraction definitions for measurement of airborne particles). Particles ≤ 50 µm correspond to both respirable and thoracic fractions, but the one of concern for crystalline silica is the respirable (≤ 10 µm).

Regarding the description of the identity of the active substance "Aluminium Silicate (aka kaolin)", currently, the CAS No (1332-58-7) and the EC No (310-194-1) are used, which correspond to the hydrous aluminium silicate. However, based on the available data (Vol. 3, B1) the actual technical material, under consideration for the renewal, is the calcined aluminium silicate (anhydrous/amorphous aluminium silicate) with CAS No 92704-41-1 and EC No 296-473-8. Thus, the RMS has proposed the change of the CAS and EC Numbers. For more details see, also Vol 4, C.1.3.2.

Based on the above, the present RAR concerns the renewal of the active substance currently approved as "Aluminium Silicate (aka kaolin)", which should be renamed to "Aluminium silicate calcined". It is noted that in all cases where "aluminum silicate" is mentioned this refers to the "aluminium silicate calcined" unless otherwise stated.

The representativeness of the batches tested in the mammalian toxicology studies has been addressed in Volume 4, point C.1.4.

- **Evaluations carried out under other regulatory contexts**

For aluminium silicate calcined CAS No 92704-41-1, referred as Kaolin, calcined, the following are included in the "Substance information" available at the ECHA website (https://echa.europa.eu/substance-information/-/substanceinfo/100.087.663):

Hazard classification & labelling

According to the notifications provided by companies to ECHA in REACH registrations no hazards have been classified.

About this substance

This substance is manufactured and/or imported in the European Economic Area in 10 000+ tonnes per year. This substance is used at industrial sites.

Consumer Uses

ECHA has no public registered data indicating whether or in which chemical products the substance might be used. ECHA has no public registered data on the routes by which this substance is most likely to be released to the environment.

Widespread uses by professional workers

ECHA has no public registered data indicating whether or in which chemical products the substance might be used. ECHA has no public registered data on the types of manufacture using this substance. ECHA has no public registered data on the routes by which this substance is most likely to be released to the environment.

Uses at industrial sites

This substance is used in the following products: pH regulators and water treatment products and laboratory chemicals.

This substance is used in the following areas: formulation of mixtures and/or re-packaging.

This substance is used for the manufacture of chemicals.

Release to the environment of this substance can occur from industrial use: in processing aids at industrial sites, as an intermediate step in further manufacturing of another substance (use of intermediates) and as processing aid.

In the REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation) Registered substances factsheets[1], there are no toxicity studies with the compound itself. Instead, the assessment of selected end-points is based on read-across from "Kaolin clay" that is considered to be a supporting substance (structural analogue or surrogate). It is noted however that the registration dossier concerns a UVCB substance and the relevance of these data for aluminium silicate calcined is considered questionable.

- **Literature search**

A search of the scientific peer reviewed open literature has been carried out by both notifiers for aluminium silicate (kaolin) in compliance with Article 8.5 of Regulation (EC) No 1107/2009 and Part A of Commission Regulation (EU) No 283/2013. The approach followed for the systematic literature search was generally in line with the principles described in the EFSA Guidance on *"Submission of scientific peer-reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009"* (EFSA Journal 2011; 9(2):2092).

Although limitations have been identified in the literature search of both applicants the RMS concludes that overall no information is identified which would impact the outcome of the risk assessment. The RMS summary of the notifiers' literature search is presented below:

Literature search by Tessenderlo Group N.V.

The literature search conducted by the Tessenderlo Group N.V. covered a duration of at least 10 years and it was performed on several databases (CAB, PubMed, Toxnet and Science Direct). In addition, relevant documents from Google, Google Scholar, ECHA, ResearchGate and the United States Environmental Protection agency database were considered. The search was performed on the following common names and CAS numbers: Kaolinite (CAS No. 1318-74-7), Kaolin (CAS No. 1332-58-7) and Kaolin, calcined (CAS No. 92704-41-1).

There is no detailed description of the relevance criteria considered in the selection process. Non-peer reviewed literature was dismissed from the search. Selection of relevant literature was performed considering text mining. Only documents that specifically mentioned toxic effects of kaolin or its common variants, were identified as positive results. Identification of key words such as dietary exposure, were considered.

The results of the literature search may briefly be outlined as follows:

Data requirement(s) captured in the search	**Number**
Number of documents retrieved from literature search (including duplicates)	14,796
Number of document excluding non peer reviewed literature	14,120
Number of documents identified as potentially relevant by text mining	301
Number of relevant articles	1
Number of articles included in the dossier	0

Not all 301 documents identified as potentially relevant by text mining are listed in the documents provided by the applicant.

[1] https://echa.europa.eu/nl/registration-dossier/-/registered-dossier/13356/7/2/2

The one article identified as relevant was a WHO review (2005)[2]. Detailed assessment of this review was not included in the dossier since all studies quoted in this review are old (none post-2003, most pre-1990). Nevertheless, the review itself may be used as supporting evidence since it suggests that kaolin is not acutely toxic, not toxic to reproduction, not genotoxic and not carcinogenic when not contaminated with crystalline silica.
The detailed literature search methodology and results are included in Section B.6 – Appendix III regarding the literature search performed by Tessenderlo Group N.V.

Literature search by SOKA

The search ranged up to at least 10 years of the submission date and included the compound aluminium silicate, CAS No. 1332-58-7. The following relevance criteria were considered for the selection of relevant articles:

1. The test system, target crop, or species are prescribed by regulation (EC) No 1107/2009 or the relevance is explained if not standard.
2. Well identified test material, including its purity and impurity profile is described
3. Study design and/or execution are consistent with relevant study guidelines
4. The endpoint is relevant to an EU data point as prescribed by Commission Regulation (EU) No 283/2013 and No 284/2013
5. Description of the observations, examinations, analysis performed, or necropsy are well described.
6. The conditions of exposure should be from legally registered use of the product.

The results of the literature search may briefly be outlined as follows:

Data requirement(s) captured in the search	Number
Total number of summary records retrieved after all searches of peer-reviewed literature (excluding duplicates)	74
Number of records excluded from the search results after rapid assessment for relevance	70
Total number of full text documents assessed in detail	4
Number of studies excluded from the dossier after detailed assessment for relevance	3
Number of studies included in the dossier	1

The detailed literature search methodology and results are included in Section B.6 – Appendix IV regarding the literature search performed by SOKA.

DAR (2008)

Kaolin is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not become bioavailable when ingested. Experience has shown it is not absorbed through the gut wall.

Kaolin has been used, and still is used, extensively as an ingredient in anti-diarrhoeal medication. In Europe, kaolin is approved for use as an anti-caking agent in food and has the food additive number E559, with a maximum concentration of 10 g/kg. In the US kaolin is approved by the US Food and Drug Administration and can be added to foods in quantities of up to 2.5%. Kaolin is also listed in the internationally recognized Food Chemical Codex as a food ingredient.

The toxicology and metabolism of kaolin were evaluated on the basis of a few studies performed, some publications and other data available.

[2] https://www.who.int/ipcs/publications/ehc/ehc_231.pdf

The notifier SOKA has provided the following general statement for waiving absorption, distribution metabolism and excretion, short-term toxicity, long-term toxicity, genotoxicity and reproductive toxicity studies:

"Aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not become bioavailable when ingested. Aluminium silicate has been, and still is used, extensively as an ingredient in anti-diarrhoeal medication. In Europe, Aluminium silicate is approved for use as an anti-caking agent in feed and has the feed additive number E559 for all animals feeding-stuffs and all species or categories with no maximum concentration. Aluminium silicate is also listed in the internationally recognized Food Chemical Codex as a food additive. Aluminium silicate is not absorbed through gut wall, does not enter bloodstream and does not distribute in tissues. Aluminium silicate is not metabolized. In view of the inert nature of Aluminium silicate, its natural occurrence, extremely low toxicity and chronic exposure in everyday life through medicines, toiletries and natural environment no study on absorption, distribution metabolism and excretion, on short-term toxicity, long-term toxicity, genotoxicity and reproductive toxicity is required."

A similar statement is provided by the notifier Tessenderlo Group N.V.:

"Aluminium silicate (kaolin) is a natural inorganic mineral. It is inert, and insoluble in aqueous and organic solvents. It does not become bioavailable when ingested. Experience has shown it is not absorbed through the gut wall. Aluminium silicate (kaolin) has been used, and still is used, extensively as an ingredient in anti-diarrhoeal medication. In the US, kaolin is approved by the US Food and Drug Administration and can be added to foods in quantities of up to 2.5%. Kaolin is also listed in the internationally recognized Food Chemical Codex as a food ingredient. The toxicology and metabolism of aluminium silicate (kaolin) have been evaluated based on a few studies performed, some publications and other available data. Through Regulation (EU) No. 380/2012 (enforced from 1st February 2014) amending Annex II to Regulation (EC) No. 1333/2008, the use of a number of aluminium-containing food additives was restricted. Among these were calcium aluminium silicate, bentonite and aluminium silicate (kaolin), which are no longer permitted to be used as food additives within the EU.

As such, it is no longer considered appropriate to rely on such cases at renewal (which were based on kaolin being an approved food additive within the EU). Following the removal of aluminium silicate from the EU list of approved food additives, EFSA commented on the impact of the ruling on several aluminium-compound containing plant protection products (including aluminium silicate). The comments made at the '15th BfR Consumer Protection Forum' indicate that where negligible exposure is demonstrated, the continued use of aluminium silicate as an insecticide on grape vines could be supported within the EU. Furthermore, the EFSA presentation noted that "Aluminium silicate could be considered a candidate for the inclusion in Annex IV of Commission Regulation (EC) No 396/2005".

B.6.1 ABSORPTION, DISTRIBUTION, EXCRETION AND METABOLISM

The notifier SOKA submitted the following argumentation for waiving ADME testing:

"Aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not become bioavailable when ingested. In view of the inert nature of Aluminium silicate, its natural occurrence, extremely low toxicity and chronic exposure in everyday life through medicines, toiletries and natural environment no study on absorption, distribution metabolism and excretion is required. Aluminium silicate is not absorbed through gut wall, does not enter bloodstream and does not distribute in tissues. Aluminium silicate is not metabolized."

The notifier Tessenderlo Group N.V. submitted the following argumentation for waiving ADME testing:

"Aluminium silicate (kaolin) is inert, insoluble in aqueous and organic solvents and non-bioavailable. No oral absorption would be expected because of the molecular size and insolubility in water and organic solvents of the molecule. It would not therefore enter bloodstream and does not distribute in tissues. Kaolin is not metabolized.

The evidence of lack of absorption combined with the chronic human exposure to aluminium silicate (kaolin) in daily life through medicines, toiletries and the natural environment, and with the need to avoid unnecessary animal testing[3], has led Tessenderlo Group N.V. to request a waiver for ADME studies."

B.6.1.1 Absorption, distribution and excretion by oral route

Previous evaluation:	In DAR (2008)

In view of the inert nature of kaolin, its natural occurrence and chronic exposure in everyday life through medicines, toiletries and natural environment, ADME studies are not required.

Absorption, Distribution

Kaolin is not absorbed through gut wall, does not enter bloodstream and does not distribute in tissues.

Metabolism

Kaolin is not metabolized.

B.6.1.2 Absorption, distribution, metabolism and excretion by other routes

No data available. Not required.

B.6.1.3 Other ADME studies

No data available. Not required.

Summary and conclusions on absorption, distribution, excretion and metabolism studies in rats

Kaolin is not absorbed through gut wall, does not enter bloodstream and does not distribute in tissues. Kaolin is not metabolized.

The RMS agrees that Aluminium silicate as a natural inorganic mineral, it is inert, insoluble in aqueous and organic solvents and it does not become bioavailable when ingested. Consequently, it is not distributed in the tissues and it is not metabolized.

[3] Council Directive 86/609/EEC of 24 November 1986

B.6.2 ACUTE TOXICITY INCLUDING IRRITANCY AND SKIN SENSITIZATION (ANNEX IIA 5.2)

B.6.2.1 Oral

Previous evaluation:	In DAR (2008)

Reference	:	[redacted], 1997a	**Dose**	:	5000 mg/kg bw
Title of study	:	Acute oral toxicity limit test	**Vehicle**	:	36% w/w suspension in distilled water
Test substance	:	Test material: Satintone 5HB, Lot # 10146, purity: 100 % ~~kaolin clay~~aluminium silicate calcined, PSL reference no.: E61114-1R	**GLP statement**	:	Yes - 40 CFR Part 160
Administration way	:	Oral *via* gavage	**Guideline**	:	~~40 CFR Part 160~~ #81-1
Species	:	Sprague-Dawley rats, albino	**Deviations from OECD TG 401**	:	None
Group size	:	5/sex/dose	**Acceptability**		Yes
Exposure	:	Single administration	**LD_{50}**	:	Rats: > 5000 mg/kg bw

Materials and methods

A GLP-compliant study (40 CFR Part 160) has been conducted to assess the potential of Satintone 5HB to produce acute toxicity *via* the oral route. Ten Sprague-Dawley rats (5/sex) received 5000 mg/kg bw of the test item orally by gavage. The animals were observed for mortality, signs of gross toxicity and behavioural changes at least once daily for a total period of 14 days. Bodyweights were recorded prior to administration and again on Days 7 and 14. At the end of the observation period all animals were subjected to gross necropsy.

Findings

All animals survived, gained weight and appeared active and healthy. There were no sign of gross toxicity, adverse pharmacological effects or abnormal behaviour. Terminal gross necropsy findings were normal.

Table B.6.2.1-1: Acute oral toxicity of Satintone 5HB – Mortality data

Males			Females		
Dose (mg/kg bw)	**Cumulative Mortality**	**Time of death, No of animals**	**Dose (mg/kg bw)**	**Cumulative Mortality**	**Time of death No of animals**
5000	0	-	5000	0	-

Conclusions

The acute oral LD_{50} value of Satintone 5HB was found to be greater than 5000 mg/kg bw in rats (there were no mortalities). Therefore, classification is not warranted, according to the Regulation (EC) No. 1272/2008.

Previous evaluation:	In DAR (2008)

Reference	: [redacted], 1997b		**Dose**	:	5000 mg/kg bw
Title of study	: Acute oral toxicity limit test		**Vehicle**	:	30% w/w suspension in corn oil
Test substance	: Test material: M-96-018, Lot # 08145, aluminium silicate calcined, polydimethylsiloxane, PSL reference no.: E61114-2R		**GLP statement**	:	Yes - 40 CFR Part 160
Administration way	: Oral *via* gavage		**Guideline**	:	~~40 CFR Part 160~~ #81-1
Species	: Sprague-Dawley rats, albino		**Deviations from OECD TG 401**	:	None
Group size	: 5/sex/dose		**Acceptability**	:	Yes
Exposure	: Single exposure		**LD_{50}**	:	> 5000 mg/kg bw

Materials and methods

A GLP-compliant study (40 CFR Part 160) has been conducted to assess the potential of M-96-018 to produce acute toxicity *via* the oral route. Ten Sprague-Dawley rats (5/sex) received 5000 mg/kg bw of the test item orally by gavage. The animals were observed for mortality, signs of gross toxicity and behavioural changes at 1, 2, 3, and 4 hours post-dosing and at least once daily thereafter for 14 days. Individual bodyweights were recorded prior to administration and again on Days 7 and 14. At the end of the observation period all animals were subjected to gross necropsy.

Findings

All animals survived, gained weight and appeared active and healthy. There were no sign of gross toxicity, adverse pharmacological effects or abnormal behaviour. Gross necropsy findings at terminal sacrifice were normal.

Table B.6.2.1-2: Acute oral toxicity of M-96-018– Mortality data

Males			**Females**		
Dose (mg/kg bw)	**Cumulative Mortality**	**Time of death, No of animals**	**Dose (mg/kg bw)**	**Cumulative Mortality**	**Time of death No of animals**
5000	0	-	5000	0	-

Conclusion

The acute oral LD_{50} value of M-96-018 was found to be greater than 5000 mg/kg bw in rats (there were no mortalities). Therefore, classification is not warranted, according to the Regulation (EC) No. 1272/2008.

Previous evaluation:	None; submitted by SOKA for the purpose of the a.s. renewal

Reference	:	[redacted], 2016a	**Doses**	:	300, 2000 mg/kg bw
Title of study	:	Kaolin: Acute oral toxicity in the rat – fixed dose method	**Vehicle**	:	distilled water
Test substance	:	hydrous kaolin, Batch 30.03.2015, purity: 100 %	**GLP statement**	:	Yes
Administration way	:	Oral *via* gavage	**Guideline**	:	OECD 420, Method B1 bis
Species	:	Wistar rats (RccHan™:WIST)	**Deviations**	:	None
Group size	:	6 females in total	**Acceptability**	:	Yes
Exposure	:	Single administration	**Result:**	:	LD_{50} >2000 mg/kg bw

Materials and methods

The acute oral toxicity of kaolin was investigated with a study performed according to the OECD TG 420 (Fixed dose procedure).

Following a sighting test of 300 mg/kg bw and 2000 mg/kg bw administered to 1 animal per dose, a further group of 4 animals were given a single oral dose of 2000 mg/kg bw by gavage.

Clinical observations were made 30 minutes, 1, 2 and 4 hours after dosing and then daily for 14 days. Morbidity and mortality checks were made twice daily. Individual body weights were recorded on Day 0 (day of dosing) and on Days 7 and 14. At the end of the observation period all animals were subjected to gross necropsy.

Findings

No mortalities were recorded. No signs of systemic toxicity were noted during the observation period. All animals shown expected gains in body weight over the observation period. No abnormalities were noted at necropsy.

Table B.6.2.1-3: Acute oral toxicity of Kaolin – Mortality data

Dose (mg/kg bw)	Animals found dead/ Animals tested	Time of death, No of animals
300	0/1	-
2000	0/4	-

Conclusions

Under the conditions of this study, the acute oral LD_{50} of kaolin is greater than 2000 mg/kg bw and therefore, classification is not warranted according to the Regulation (EC) No. 1272/2008.

B.6.2.2 Percutaneous

Previous evaluation:	In DAR (2008)

Reference	:	[redacted], 1997c	**Dose**	:	5000 mg/kg bw
Title of study	:	Acute dermal toxicity limit test	**Vehicle**	:	50% w/w mixture in distilled water

Test substance	: Test material: Satintone 5HB, Lot # 10146, purity: 100% ~~kaolin clay~~aluminium silicate calcined, PSL reference no.: E61114-1R	**GLP statement**	: Yes - 40 CFR Part 160
		Guideline	: ~~40 CFR Part 160~~ #81-2
Administration way	: Dermal	**Deviations from OECD TG 402**	: None
Species	: Sprague-Dawley rats, albino	**Acceptability**	: Yes
Group size	: 5/sex/dose		
Exposure	: 24 hours	**LD_{50}**	: > 5000 mg/kg bw

Materials and methods:

A GLP-compliant study (40 CFR Part 160) has been conducted to assess the potential of Satintone 5HB to produce acute toxicity *via* the dermal route. Ten Sprague-Dawley rats (5/sex) received dermally 5000 mg/kg bw of Satintone 5HB. The test substance was placed on one 2x3´´, 4-ply gauze pad, then applied to a dose area of approximately 2x3´´ (approximately 10 % of the body surface). The gauze and entire trunk of each animal were wrapped with Durapore tape for 24 hours. After 24 hours, the pads were removed, and the test sites were gently wiped with water and a clean towel to remove any residual test substance. The animals were observed for signs of gross toxicity and behavioural changes at least once daily for 14 days. Bodyweights were recorded prior to application and again on Days 7 and 14. At the end of the observation period all animals were subjected to gross necropsy.

Findings:

Neither toxic symptoms nor death was observed at 5000 mg/bw dose level. There were no signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour. At gross necropsy, no visible lesions were observed.

Table B.6.2.2-1: Acute dermal toxicity of Satintone 5HB – Mortality data

Males			Females		
Dose (mg/kg bw)	**Cumulative Mortality**	**Time of death**	**Dose (mg/kg bw)**	**Cumulative Mortality**	**Time of death**
5000	0	-	5000	0	-

Conclusions

The acute dermal LD_{50} values of Satintone 5HB was found to be greater than 5000 mg/kg bw. Therefore, classification is not warranted, according to the Regulation (EC) No. 1272/2008.

Previous evaluation:	None; submitted by SOKA for the purpose of the a.s. renewal

Reference	:	[redacted]., 2016b	**Dose**	:	2000 mg/kg bw
Title of study	:	Kaolin: Acute dermal toxicity (limit test) in the rat	**Vehicle**	:	Distilled water
Test substance	:	hydrous kaolin, Batch 30.03.2015, purity: 100%	**GLP statement**	:	Yes
Administration way	:	Dermal	**Guideline**	:	OECD 402, Method B3

Species	:	Wistar rats (RccHan™:WIST)	**Deviations**	:	None
Group size	:	5/sex/dose	**Acceptability**	:	Yes
Exposure	:	24 hours, semi-occlusive	**Result:**	:	LD_{50} >2000 mg/kg bw

Materials and methods

The acute dermal toxicity of kaolin was investigated with a study performed according to the OECD TG 402 (limit test).

Initially, 2 Wistar rats (1/sex) were given a single dermal application of kaolin at 2000 mg/kg bw to intact skin, under semi-occlusive conditions, for 24 hours. Based on the results of the initial test, a further group of 8 animals (4/sex) was similarly tested. After the 24-hour contact period the bandages were carefully removed and the treated skin and surrounding hair wiped with cotton wool moistened with distilled water to remove any residual test item. The animals were observed for deaths or overt signs of toxicity 30 minutes, 1, 2 and 4 hours after dosing and subsequently once daily for 14 days. After removal of the dressings and subsequently once daily for 14 days, the test sites were examined for evidence of primary irritation. Individual body weights were recorded prior to application of the test item and on Days 7 and 14. At the end of the observation period all animals were subjected to gross necropsy.

Findings

No mortalities were recorded. No signs of systemic toxicity were noted during the 14-day observation period. There were no signs of dermal irritation. The initially treated female showed no gain in body weight during the first week and body weight loss during the second week. Two females showed body weight loss during the first week with expected gain in body weight during the second week. The remaining animals showed expected gains in body weight over the study period. No abnormalities were noted at necropsy.

Table B.6.2.2-3: Acute dermal toxicity of Kaolin – Mortality data

Dose (mg/kg bw)	Sex	Animals found dead/ Animals tested	Time of death, No of animals
2000	Males	0/5	-
	Females	0/5	-

Conclusions

Under the conditions of this study, the acute dermal LD_{50} of kaolin is greater than 2000 mg/kg bw and therefore, classification is not warranted according to the Regulation (EC) No. 1272/2008.

B.6.2.3 Inhalation

Previous evaluation:	In DAR (2008)

Reference	:	[redacted], 1997d	**Dose**	:	2.18 mg/L
Title of study	:	Acute inhalation toxicity limit test	**Vehicle**	:	Air
Test substance	:	Test material: M-96-018, PSL reference no.: E70716-4D purity: 98.8 % ~~calcined kaolin~~aluminium silicate	**GLP statement**	:	Yes - 40 CFR Part 160

	calcined, 1.2% siloxane		
Administration way	: Inhalation, whole body	**Guideline**	: ~~40 CFR Part 160~~ #81-3
Species	: Sprague-Dawley rats, albino	**Deviations from OECD TG 403**	: No justification for whole-body exposure is provided in the study report as required.
Group size	: 5/sex/dose	**Acceptability**	: Yes
Exposure	: 4 h	**LC_{50}**	: > 2.18 mg/L

Materials and methods

A GLP-compliant study (40 CFR Part 160) has been conducted to assess the potential of M-96-018 to produce acute toxicity *via* the inhalation route. After establishing the desired generation procedures during pre-test trials, ten healthy Sprague-Dawley rats (5/sex) were exposed to the test atmosphere for 4 hours. Chamber concentration and particle size distribution of the test substance were determined periodically during the exposure period. ~~Rats (whole body) were exposed to M-96-018 was administered by inhalation of a test atmosphere containing dust generated from the test substance.~~ The rats were observed for signs of gross toxicity and behavioural changes for a 14-day period following exposure. Bodyweights were recorded prior to exposure and again on Days 7 and 14. At the end of the observation period, all rats were subjected to gross necropsy.

Findings

The gravimetric and nominal concentrations were 2.18 mg/L and 3.75 mg/L, respectively. The Mass Mean Aerodynamic Diameter (MMAD) was approximately 2.0 µm ± 2.0. The achieved concentration is considered acceptable since it exceeds the limit concentration of 2.0 mg/L indicated in the OPP 81–3 Guideline and it is also in line with the specific considerations for classification of substances as acutely toxic by the inhalation route of the CLP (Inhaled particles MMAD: 1-4 microns, maximum dose 2 mg/L).

There were no deaths during the study. During the first hour of exposure, animals exhibited ocular and nasal discharge, hunched posture and hypoactivity. Upon removal from the exposure chamber ocular and nasal discharge persisted in all animals. All rats recovered from these symptoms within 17 hours and appeared active and healthy for the remainder of the study. All animals gained bodyweight over the 14-day observation period. There were no observable abnormalities at gross necropsy.

Ocular effects and clinical signs may be attributed to the whole-body mode of exposure to the test material.

Table B.6.2.3-1: Summary of particle size distribution

Sample No.	Time of Sample	Collection time (minutes)	Mass Median Aerodynamic Diameter (µm)	Geometric Standard deviation
1	1.5 hours	1	1.9	1.99
2	3 hours	1	2.0	2.00

Table B.6.2.3-2: Acute inhalation toxicity of M-96-018 – Mortality data

Males			Females		
Dose (mg/L)	**Cumulative Mortality**	**Time of death**	**Dose (mg/L)**	**Cumulative Mortality**	**Time of death**
2.18	0	-	2.18	0	-

Conclusions

The acute LC_{50} by inhalation of M-96-018 in albino rats was determined to be greater than 2.18 mg/L. Therefore, classification is not warranted, according to the Regulation (EC) No. 1272/2008.

Previous evaluation:	In DAR (2008)

Reference	: [redacted], 1997e	**Exposure**	: 4 h
Title of study	: Acute inhalation toxicity limit test	**Dose**	: 2.07 mg/L
Test substance	: Test material: M-97-009, Lot # 09255, PSL reference no.: E70704-3D purity: 100 % ~~calcined kaolin~~ aluminium silicate calcined	**Vehicle**	: Air
		GLP statement	: Yes - 40 CFR Part 160
		Deviations from OECD TG 403	: No justification for whole-body exposure is provided in the study report as required.
Administration way	: Inhalation, whole body	**Guideline**	: ~~40 CFR Part 160~~ #81-3
Species	: Sprague-Dawley rats, albino	**Acceptability**	: Yes
Group size	: 5/sex/dose	**LC_{50}**	: > 2.07 mg/L

Materials and methods

A GLP-compliant study (40 CFR Part 160) has been conducted to assess the potential of calcinated kaolin to produce acute toxicity *via* the inhalation route. After establishing the desired generation procedures during pre-test trials, ten healthy Sprague-Dawley rats (5/sex) were exposed (whole body) to the test atmosphere for 4 hours. Chamber concentration and particle size distribution of the test substance were determined periodically during the exposure period. ~~Rats (whole body) were exposed to M-97-009 was administered by inhalation of a test atmosphere containing dust generated from the test substance.~~ The rats were observed for signs of gross toxicity and behavioural changes for a 14 days period following exposure. Bodyweights were recorded prior to exposure and again on Days 7 and 14. At the end of the observation period, all rats were subjected to gross necropsy.

Findings

The gravimetric and nominal chamber concentrations were 2.07 mg/L and 10.77 mg/L, respectively. The mass median aerodynamic diameter (MMAD) was estimated to 2.5 microns. The achieved concentration is considered acceptable since it exceeds the limit concentration of 2.0 mg/L indicated in the OPP 81–3 Guideline and it is also in line with the specific considerations for classification of substances as acutely toxic by the inhalation route of the CLP (Inhaled particles MMAD: 1-4 microns, maximum dose 2 mg/L).

There were no deaths during the study. During the initial 2.5 hours of exposure, animals exhibited ocular and nasal discharge, irregular respiration, hunched posture and hypoactivity. Upon removal from the exposure chamber ocular and nasal discharge persisted in all animals. Hunched posture also remained in one animal. All rats recovered from these symptoms within 17 hours and appeared active

and healthy for the remainder of the study. All animals gained bodyweight over the 14-day observation period. There were no observable abnormalities at gross necropsy.

Ocular effects and clinical signs may be attributed to the whole-body mode of exposure to the test material.

Table B.6.2.3-3: Summary of particle size distribution

Sample No.	Time of Sample	Collection time (minutes)	Mass Median Aerodynamic Diameter (µm)	Geometric Standard deviation
1	1.5 hours	2	2.5	2.22
2	3 hours	2	2.5	2.22

Table B.6.2.3-4: Acute inhalation toxicity of M-97-009 – Mortality data

Males			Females		
Dose (mg/L)	Cumulative Mortality	Time of death	Dose (mg/L)	Cumulative Mortality	Time of death
2.07	0	-	2.07	0	-

Conclusions

The acute LC_{50} by inhalation of M-97-009 in albino rats was determined to be greater than 2.07 mg/L. Therefore, classification is not warranted, according to the Regulation (EC) No. 1272/2008.

Previous evaluation:	None; submitted by SOKA for the purpose of the a.s. renewal

Reference	:	[redacted], 2016	**Vehicle**	:	Air
Title of study	:	Kaolin: Acute inhalation toxicity (nose only) study in the rat	**GLP statement**	:	Yes
Test substance	:	hydrous kaolin, Batch 30.03.2015, purity: 100%	**Guideline**	:	OECD 436, Method B.52
Administration way	:	nose-only	**Deviation**	:	The archiving statement has been amended to reflect the fact that no specimens were retained during this study. This deviation is considered to have not affected the integrity or validity of the study.
Species	:	Wistar rats (RccHan™:WIST)			
Group size	:	3/sex/dose			
Exposure	:	4 hours	**Acceptability**	:	Yes
Dose	:	5.07 mg/L	**Result**	:	LC_{50} > 5.07 mg/L

Materials and methods

The acute inhalation toxicity of kaolin was investigated with a study performed according to the OECD TG 436 (Acute toxic class method).

A group of 6 rats (3/sex) was exposed to kaolin at a nominal dust atmosphere of 8.68 mg/L. The animals were exposed for 4 hours using a nose only exposure system, followed by a 14-day observation period. The particle size of the generated atmosphere inside the exposure chamber was

determined three times during the exposure period. All animals were observed for clinical signs at hourly intervals during the exposure, immediate on removal from the restraining tubes at the end of exposure, 1 hour after termination of exposure and subsequently once daily for 14 days. Any evidence of overt toxicity was recorded at each observation. Individual body weights were recorded prior to treatment and on Days 1, 3, 7 and 14. At the end of the observation period, all animals were subjected to gross necropsy.

Findings

The mean achieved atmosphere concentration was 5.07 mg/L. No mortalities were recorded. Common abnormalities noted during the study included decreased respiratory rate, hunched posture, pilo-erection, red/brown staining around the snout and wet fur. Animals recovered to appear normal on Day 2 post-exposure. No macroscopic abnormalities were detected at necropsy.

Table B.6.2.3-5: Acute inhalation toxicity of Kaolin – Mortality data

Mean achieved atmosphere concentration (mg/L)	Sex	Animals found dead/ Animals tested	Time of death, No of animals
5.07	Males	0/3	-
	Females	0/3	-

Table B.6.2.3-6: Particle size distribution

Mean Mass Median Aerodynamic Diameter (µm)	Geometric Standard Deviation	Predicted amount less than 4µm (%)
3.13	2.42	61.0

Conclusions

Under the conditions of this study, the acute inhalation LC_{50} of kaolin is greater than 5.07 mg/L (mean achieved concentration) and therefore, classification is not warranted according to the Regulation (EC) No. 1272/2008.

B.6.2.4 Skin irritation

Previous evaluation:	In DAR (2008)

Reference	:	[redacted]., 1997f	**Dose**	:	500 mg/animal
Title of study	:	Primary skin irritation	**Vehicle**	:	50% w/w mixture in distilled water
Test substance	:	Test material: M-96-018, Lot # 08145, aluminium silicate calcined, polydimethylsiloxane, PSL reference no.: E61114-2R	**GLP statement**	:	Yes - 40 CFR Part 160
Administration way	:	Dermal	**Guideline**	:	~~40 CFR Part 160~~ #81-5
Species	:	New Zealand rabbits, albino	**Deviations from OECD TG 404**	:	None
Group size	:	3/sex/dose	**Acceptability**	:	Yes
Exposure	:	4 h	**Result**	:	Non-irritant

Materials and methods

The test substance was applied to one 6 cm^2 intact dose site on each animal and covered with a 1x1", 4-ply gauze pad. The pad and entire trunk of each animal were then wrapped with semi-occlusive 3" Micropore tape and held in place for 4 hours. At the end of the exposure period, the pads were removed, and the test sites were gently wiped with water and a clean towel, to remove any residual test substance. Examination of dermal reactions was performed at 1, 24, 48, 72 hours post application according to the Draize scoring system.

Findings

No dermal irritation was noted at any treated site during the study. All animals appeared active and healthy. There were no signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour.

Table 6.2.4-1: Individual and mean scores for erythema (E) and oedema (O)

Animal No	Hours after patch removal				Mean score (24-72h)
	1	24	48	72	
	E/O	E/O	E/O	E/O	E/O
1	0/0	0/0	0/0	0/0	0/0
2	0/0	0/0	0/0	0/0	0/0
3	0/0	0/0	0/0	0/0	0/0
4	0/0	0/0	0/0	0/0	0/0
5	0/0	0/0	0/0	0/0	0/0
6	0/0	0/0	0/0	0/0	0/0

Conclusions

Under the conditions of this study, M-96-018 is not a skin irritant. Therefore, classification is not warranted according to the Regulation (EC) No. 1272/2008.

B.6.2.5 Eye irritation

Previous evaluation:	In DAR (2008)

Reference	: [redacted], 2000	**Dose**	: 0.1 ml/animal (40-50 mg)
Title of study	: Primary eye irritation study in rabbits	**Vehicle**	: -
Test substance	: Test material: Surround WP, Lot # 02140, ~~purity~~ content: 95% ~~kaolin~~ aluminium silicate calcined, PSL reference no.: E01110-1D	**GLP statement**	: Yes - 40 CFR Part 160
		Guideline	: ~~40 CFR Part 160~~ OPPTS 870.2400 (1998)
Administration way	: Eye	**Deviation from OECD TG 405**	: None

Species	: New Zealand rabbits, albino	**Acceptability**	: Yes
Group size	: 3/dose (1 male and 2 females)		
Exposure	: Single instillation	**Result**	: ~~Slightly irritant to eyes~~ Non-irritant

Materials and methods

A GLP-compliant eye irritation test was conducted to 3 New Zealand albino rabbits, according to OPPTS 870.2400 (1998).

Surround WP was instilled into the conjunctival sac of the right eye of each rabbit. The upper and lower lids were then gently held together for about one second before releasing to minimize loss of the test substance. The other eye of each rabbit remained untreated with the test substance and served as a control. Examination of the ocular responses was made 1, 24, 48, 72 hours after exposure and evaluated according to the Draize scheme.

Findings

All animals appeared active and healthy. No corneal opacity or iritis was noted during the study. One hour after instillation of Surround WP, all treated eye exhibited conjunctivitis. The incidence and severity of irritation decreased thereafter. All animals were free ocular irritation by 48 hours.

Table B.6.2.5-1: Individual and mean ocular irritation scores after application of Surround WP

Animal No.	Ocular reaction	Hours after application				Mean scores 24-72 h
		1	24	48	72	
1	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	1	1	0	0	0.33
	Conjunctival chemosis	1	0	0	0	0
2	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	1	0	0	0	0
	Conjunctival chemosis	0	0	0	0	0
3	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	1	0	0	0	0
	Conjunctival chemosis	0	0	0	0	0

Conclusions

Under the conditions of this study, the test item was not found irritant to rabbit eye and therefore, classification is not warranted, according to the Regulation (EC) No. 1272/2008.

Previous evaluation:	In DAR (2008)

Reference	:	[redacted], 1997g	**Dose**	:	0.1 ml/animal (40-50 mg)
Title of study	:	Primary eye irritation	**Vehicle**	:	-

Test substance	:	Test material: M-96-018, Lot # 08145, aluminium silicate calcined, polydimethylsiloxane, PSL reference no.: E61114-2R	**GLP statement**	:	Yes - 40 CFR Part 160
Administration way	:	Eye	**Guideline**	:	~~40 CFR Part 160~~ #81-4
Species	:	New Zealand rabbits, albino	**Deviations from OECD TG 405**	:	None
Group size	:	6/dose (group I), 3/dose (group II) females	**Acceptability**	:	Yes
Exposure	:	Group I: unrinsed Group II: rinsed 20-30 seconds after instillation	**Result**	:	~~Slight irritant to eyes~~ Non-irritant

Materials and methods

A GLP-compliant eye irritation test was conducted to 9 female New Zealand albino rabbits.

M-96-018 was instilled into the conjunctival sac of the right eye of each rabbit. The upper and lower lids were then gently held together for about one second before releasing to minimize loss of the test substance. The other eye of each rabbit remained untreated with the test substance and served as a control.

Group I (6 rabbits): The treated eyes of six rabbits were not rinsed after instillation.

Group II (3 rabbits): The treated eyes of three rabbits were rinsed with physiological saline approximately 20-30 seconds after instillation.

Examination of the ocular responses was made 1, 24, 48, 72 hours after exposure, according to the Draize scheme. The animals were also observed for signs of gross toxicity and behavioural changes at least once daily during the test period.

Findings

All animals appeared active and healthy. There were no signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour. No corneal opacity or iritis was noted during the study. One hour after instillation of M-96-018, all treated eyes (unrinsed and rinsed) exhibited conjunctivitis. The incidence and severity of irritation decreased thereafter. All rinsed and unrinsed eyes were free irritation by 24 and 72 hours.

Table B.6.2.5-2: Individual and mean ocular irritation scores in animals of Group I (unrinsed eyes)

Animal No.	Ocular reaction	Hours after application				Mean scores 24-72 h
		1	24	48	72	
1	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	3	2	1	0	1
	Conjunctival chemosis	1	1	0	0	0.33
2	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	2	1	0	0	0.33
	Conjunctival chemosis	0	0	0	0	0
3	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0

	Conjunctival redness	2	1	0	0	0.33
	Conjunctival chemosis	1	0	0	0	0
4	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	2	0	0	0	0
	Conjunctival chemosis	1	0	0	0	0
5	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	3	2	1	0	1
	Conjunctival chemosis	1	0	0	0	0
6	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	2	1	0	0	0.33
	Conjunctival chemosis	0	0	0	0	0

Table B.6.2.5-3: Individual and mean ocular irritation scores in animals of Group II (rinsed eyes)

Animal No.	Ocular reaction	Hours after application				Mean scores 24-72 h
		1	24	48	72	
1	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	1	0	0	0	0
	Conjunctival chemosis	0	0	0	0	0
2	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	2	0	0	0	0
	Conjunctival chemosis	0	0	0	0	0
3	Corneal opacity	0	0	0	0	0
	Iritis	0	0	0	0	0
	Conjunctival redness	1	0	0	0	0
	Conjunctival chemosis	0	0	0	0	0

Conclusions

Under the conditions of this study, M-96-018 was not found to be irritant to the rabbit eye and therefore, classification is not warranted, according to the Regulation (EC) No. 1272/2008.

B.6.2.6 Skin sensitisation

Previous evaluation:	None; submitted by SOKA for the purpose of the a.s. renewal

Reference	:	[redacted]., 2016c	**Vehicle**	:	Ethanol/distilled water (7:3)
Title of study	:	Kaolin: local lymph node assay in the mouse – pooled method	**GLP statement**	:	Yes

Test substance	:	Test material: hydrous kaolin, Batch 30.03.2015, purity: 100 % kaolin	**Guideline**	:	OECD 429; Method B.42
Administration way	:	Local lymph node	**Deviations**	:	It is not stated in the study report if the highest concentration used maximises exposure, whilst in the pre-screen test local skin irritation was not demonstrated.
Species	:	CBA/CA (CBA/CaOlaHsd) mice			
Group size	:	4 females/group			
Exposure	:	3 days	**Acceptability**	:	Yes
Dose	:	25%, 10%, 5%	**Result**	:	Not sensitising

Materials and methods

A Local Lymph Node Assay has been performed to assess the potential of kaolin to cause skin sensitisation to CBA/Ca mice, according to OECD TG 429.

The selection of doses for the main study was based on a preliminary screening test.

For the main study, three groups of 4 animals, were treated daily for three consecutive days (Day 1, 2, 3) with 50 µL (25 µL/ear) of the test item in ethanol/distilled water 7:3 at concentrations of 25%, 10% or 5% w/w. The test item was administered using an automatic micropipette and spread over the dorsal surface of the ear using the tip of the pipette. A further group of 4 animals received the vehicle alone (ethanol/distilled water 7:3) under the same procedure. On Day 6, all mice were injected *via* the tail vein with 250 µL of phosphate buffered saline (PBS) containing ^{3}H-methyl thymidine, giving a total of 20 µCi to each mouse.

Five hours after the administration of ^{3}HTdR, all mice were killed, and the draining auricular lymph nodes were excised and pooled for each experimental group. For each group 1 mL of PBS was added to the pooled lymph nodes.

All animals were observed twice daily on Days 1, 2 and 3 and on a daily basis on Days 4, 5 and 6. Any sign of toxicity or sign of ill health during the test were recorded. Individual body weights were recorded prior to treatment and on Day 6.

The proliferation response of lymph node cells was expressed as the number of radioactive disintegrations per minute per lymph node and as the ration of ^{3}HTdR incorporation into lymph node cells of tested nodes relative to that recorded for the control nodes (Stimulation Index - SI).

Findings

No animal died during the study. No signs of systemic toxicity were noted in the test or control animals. Bodyweight change of the test animals between Day 1 and Day 6 was comparable to that observed in the corresponding control group animals over the same period.

The radioactive disintegrations per minute per lymph node and the SI values are presented in the table below:

Concentration in ethanol/distilled water 7:3 (%w/w)	dpm	dpm/node	Stimulation Index
Vehicle	2802.09	350.26	n.a.
5	2251.88	281.49	0.80
10	1662.87	207.86	0.59
25	3960.19	495.02	1.41

* disintegrations per minute
** disintegrations per minute/node obtained by dividing the disintegrations per minute value by 8 (total number of lymph nodes)

Reliability check

The sensitivity of the strain of mouse used for the LLNA has been assessed according to the OECD 406. A group of five animals was treated with 50 µL (25 µL/ear) of α-hexylcinnamaldehyde tech. 85% as an emulsion in ethanol/distilled water 7:3 at a concentration of 15% v/v. The SI was calculated at 9.13, indicating a positive response.

Conclusions

Under the conditions of this study, kaolin was not found to be sensitising to mouse skin and therefore, classification is not warranted according to the Regulation (EC) No. 1272/2008.

Due to uncertainty raised regarding the acceptability of the maximum dose tested, the study is considered to be supportive to the second skin sensitisation assay available.

Previous evaluation:	None; submitted by Tessenderlo Group N.V. for the purpose of the a.s. renewal

Reference	:	[redacted], 2017	**Vehicle**	:	Physiological saline
Title of study	:	Assessment of sensitising properties on albino guinea pigs. Maximisation test according to Magnusson and Kligman (SMK-PH-17/0024)	**GLP statement**	:	Yes
Test substance	:	M-99-SPI (aluminium silicate calcined, purity: 99%)	**Guideline**	:	OECD 406; Method B.6
Administration way	:	Induction: Intradermal and topical application Challenge: Topical application	**Deviations**	:	Semi-occlusive dressing was used, which however does not compromise the validity of the study
Species	:	Guinea pig, Dunkin-Hartley			
Group size	:	10/test group; 5/control group	**Acceptability**	:	Yes
Dose	:	Induction: 10% intradermal; 40% topical Challenge: 40%, 20% topical	**Result**	:	Not sensitising

Materials and methods

A guinea pig maximisation test has been performed to assess the skin sensitisation potential of M-99-SPI, according to OECD TG 406.

The doses selected for the main study were based on preliminary tests conducted for the determination of the maximal non-necrotising concentration (MNNC), the pre-maximal non-irritant concentration (pre-MNIC) and the maximal non-irritant concentration (MNIC).

The main study was conducted as follows:

Induction: Intradermal injections

Day 0 – treated group (10 animals)

Three pairs of intradermal injections of 0.1 mL were performed on the scapular zone in such a way to ensure that each pair was placed on either side of the spine, as follows:

Injection 1: Freund's Complete Adjuvant (FCA) diluted at 50% in physiological saline

Injection 2: the test item M-99-SPI at 10% in physiological saline

Injection 3: a test mixture in equal volumes FCA at 50% and the test item M-99-SPI at 20% in physiological saline

Day 0 – control group (5 animals)

Three pairs of intradermal injections of 0.1 mL volume were given in the same sites as in the treated group, as follows:

Injection 1: FCA diluted at 50% in physiological saline

Injection 2: physiological saline

Injection 3: a mixture with equal volumes of FCA at 50% and physiological saline

Induction: Topical application

Day 7 – treated and control groups

The scapular zone of all the animals in each group was brushed with a solution of sodium lauryl sulphate at 10% in thick vaseline, in order to create local irritation.

Day 8 – treated group

0.5 mL of the test item M-99-SPI at 40% in distilled water was applied on the injection sites of each animal under occlusive dressing and held in contact for 48 hours.

Day 8 – control group

0.5 mL of distilled water was applied on the injection sites of each animal under occlusive dressing and held in contact for 48 hours.

Challenge: Topical application

Day 21 – treated and control groups

All animals received one sample cup containing the test item diluted at 40% and one sample cap containing the test item diluted at 20% in distilled water. The patches were held in place for 24 hours.

Day 22 – treated and control groups

The treated areas were rinsed with distilled water after the removal of the semi-occlusive dressing.

Observations were made 24 and 48 hours after patch removal.

Findings

No cutaneous reaction was noted during the induction phase in the control group. In the test group, moderate erythema was noted in all animals 24 hours after the first induction. Furthermore, discrete erythema associated with dryness of the skin was noted in all animals 24 hours after the second induction.

In the treated group (treatment dose of 20%), no macroscopic cutaneous reactions attributable to skin sensitisation were noted after the challenge phase. In the concurrent control group, no macroscopic cutaneous intolerance reactions were recorded.

In the treated group (treatment dose of 40%), no macroscopic cutaneous reactions attributable to skin sensitisation were noted after the challenge phase. In the concurrent control group, no macroscopic cutaneous intolerance reactions were recorded.

There was no mortality during the study. No abnormality in bodyweight gain was recorded in either of the groups.

Table B.6.2.6-1: Skin sensitising response indices after challenge exposure

Challenge concentration	Tested group	Animals with positive responses/total number of animals	
		24 hours after dressing removal	48 hours after dressing removal
40%	Treated animals	0/10	0/10
	Control group	0/5	0/5
20%	Treated animals	0/10	0/10
	Control group	0/5	0/5

Reliability check

Three tests with the reference substance α-hexylcinnamaldehyde have been performed to assess the sensitivity of the guinea pig strain used for this study. The results of these experiments showed a skin sensitising potential of α-hexylcinnamaldehyde.

Conclusions

Under the conditions of this study, M-99-SPI was found to be not sensitising to guinea pig skin and therefore, classification is not warranted according to the Regulation (EC) No. 1272/2008.

B.6.2.7 Phototoxicity

According to the data requirements listed in Reg. (EU) No. 283/2013, an *"in vitro phototoxicity study shall be required where the active substance absorbs electromagnetic radiation in the range 290-700 nm and is liable to reach the eyes or light-exposed areas of skin, either by direct contact or through systemic distribution".* Furthermore, for an active substance fulfilling the above criteria, *"if the Ultraviolet/visible molar extinction/absorption coefficient is less than 10 L × mol^{-1} × cm^{-1}, no toxicity testing is required"*.

According to Tessenderlo Group N.V., due to insolubility and lack of volatility of kaolin, it is not feasible to perform UV/VIS spectra and thus, no molar extinction coefficient can be calculated. Therefore, a waiver is proposed for this data requirement.

The applicant SOKA had informed the RMS that a test for the determination of Spectra (UV/VIS, IR, NMR, MS) of aluminium silicate calcined was on-going. Later in the process, the RMS was informed that the expected study was not performed due to insolubility and lack of volatility of aluminium silicate. The following waiver is proposed for this data requirement by the notifier SOKA:

"Due to insolubility and lack of volatility of aluminium silicate, it is not feasible to perform UV/VIS spectra and thus, no molar extinction coefficient can be calculated. Therefore, a waiver is proposed for this data requirement."

The notifiers' waivers are considered acceptable by the RMS, since it is not technically feasible to conduct a phototoxicity study due to the physicochemical properties of aluminium silicate. Aluminium silicate is an inert, insoluble dust and there is no guideline available for the testing of phototoxicity of insoluble substances.

It is also noted that a UV/VIS absorption spectra study was not performed for the Annex I inclusion of the active substance "*Due to insolubility and lack of volatility"*. A max. UV/VIS absorption endpoint in the DAR (2008) and in the subsequent EFSA Conclusion [EFSA Journal 2012;10(1):2493] was *"Not applicable"*.

A similar approach has recently been considered for the active substance kieselgur (EFSA, 2020).

Summary and conclusions on acute toxicity studies

The acute toxicity of aluminium silicate calcined was based on the studies presented in the DAR (2008) and re-evaluated by the RMS. Among the five new studies submitted for the renewal of the active substance, only one was performed with aluminium silicate calcined (amorphous). The other four studies were conducted with hydrous kaolin (crystalline) which is considered worst-case from a toxicological point of view (see Volume 4 – CONFIDENTIAL).

Kaolin calcined was found to be of low toxicity *via* the oral and the dermal route. The acute inhalation studies performed, indicated an LC_{50} > 5.07 mg/L/4h (nose-only). According to the available studies, kaolin calcined caused no irritation to rabbit skin and eyes. Finally, the test substance lacks skin sensitisation properties, as indicated in the available LLNA and GPMT tests. A summary of the available acute toxicity data is presented in Tables B.6.2-1 to B.6.2-3.

Table B.6.2-1: Acute toxicity studies

Test substance	**LD_{50}/LC_{50}** (mg/kg bw or mg/L)	**Species**	**Route**	**Reference**
Satintone 5HB, Lot # 10146, purity: 100 % ~~kaolin clay~~ aluminium silicate calcined	> 5000	Rat / SD	Oral	[redacted] 1997a
M-96-018, Lot # 08145, aluminium silicate calcined, polydimethylsiloxane ~~purity: 98.8% calcined kaolin~~	> 5000	Rat / SD	Oral	[redacted], 1997b
hydrous kaolin, Batch 30.03.2015, purity: 100 %	> 2000	Rat / Wistar	Oral	[redacted], 2016a
Satintone 5HB, Lot # 10146, purity: 100% ~~kaolin clay~~ aluminium silicate calcined	> 5000	Rat / SD	Dermal	[redacted], 1997c
hydrous kaolin, Batch 30.03.2015, purity: 100 %	> 2000	Rat / Wistar	Dermal	[redacted], 2016b

Test substance	LD_{50}/LC_{50} (mg/kg bw or mg/L)	Species	Route	Reference
M-96-018, purity: 98.8 % ~~calcined kaolin~~ aluminium silicate calcined, 1.2% siloxane	> 2.18	Rat / SD	Inhalation	[redacted], 1997d
M-97-009, Lot # 09255, 100% aluminium silicate calcined	> 2.07	Rat / SD	Inhalation	[redacted], 1997e
hydrous kaolin, Batch 30.03.2015, purity: 100%	> 5.07	Rat / Wistar	Inhalation	[redacted], 2016

Table B.6.2-2: Skin and eye irritation studies

Test substance	Effect	Species	Route	Reference
M-96-018, Lot #08145, aluminium silicate calcined, polydimethylsiloxane	Not irritating to skin	Rabbit / NZW	Dermal	[redacted]., 1997f
M-96-018, Lot #08145, aluminium silicate calcined, polydimethylsiloxane	Not irritating to eyes	Rabbit / NZW	Ocular	[redacted]., 1997g
Surround WP, Lot #02140, content: 95% kaolin	Not irritating to eyes	Rabbit / NZW	Ocular	[redacted], 2000

Table B.6.2-3: Skin sensitisation studies

Test substance	Effect	Species	Reference
hydrous kaolin, Batch 30.03.2015, purity: 100%	Not sensitising	Mouse / CBA/Ca	[redacted], 2016c
M-99-SPI, aluminium silicate calcined, purity: 99%	Not sensitising	Guinea pig / Dunkin-Hartley	[redacted], 2017

B.6.3 SHORT-TERM TOXICITY (ANNEX IIA 5.3)

No short-term oral toxicity study on Kaolin calcined is available.

In the DAR (2008), the Notifier Tessenderlo Group N.V. requested that a waiver for short-term toxicity studies be granted for kaolin in view of its excellent safety record based on continuous use as a food additive, pharmaceutical ingredient, personal hygiene component and in many industrial applications. In the renewal dossier, Tessenderlo Group N.V. presented the same argument for waiving short term toxicity studies.

The applicant SOKA did not provide any short-term toxicity data based on the following justification:

"Aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not become bioavailable when ingested. Aluminium silicate has been, and still is used, extensively as an ingredient in anti-diarrhoeal medication. In Europe, Aluminium silicate is approved for use as an anti-caking agent in feed and has the feed additive number E559 for all animals feedingstuffs and all species or categories with no maximum concentration. Aluminium silicate is also listed in the internationally recognized Food Chemical Codex as a food additive. In view of the inert nature of Aluminium silicate, its natural occurrence, extremely low toxicity and chronic exposure in everyday life through medicines, toiletries and natural environment no short-term toxicity study is required."

B.6.3.1 Oral 28-day study

No data available. See justification, above (B.6.3).

B.6.3.2 Oral 90-day study

No data available. See justification, above (B.6.3).

B.6.3.3 Other routes

Previous evaluation:	None; submitted by SOKA for the purpose of the a.s. renewal

The notifier SOKA has conducted a 2 week-toxicity study by inhalation administration to Han Wistar rats. The purpose of this study was to assess the local and systemic toxic potential of Kaolin or Kaolinitic Clay for commercial use.

Reference	:	[redacted], 2019	**Exposure**	:	6 hours, 5 days each week.
Title of study	:	Kaolin and Kaolinitic Clay: Toxicity Study by Inhalation Administration to Han Wistar Rats for 2 Weeks	**Doses**	:	25, 50 and 110 µg/L
Test substance	:	Kaolin (92,3% Kaolinite; 0,8% Quartz) and Kaolinitic clay (75,3% Kaolinite; 17% Quartz) *	**Vehicle**	:	Air
Administration way	:	Repeated inhalation for 2 weeks – snout only exposure	**GLP statement**	:	Yes
Species	:	Wistar (RccHan™:WIST) strain rats	**Guideline**	:	Not applicable
Group size	:	10/sex/dose	**Acceptably**	:	Yes

* Data on the composition of clays are reported for information only, since according to the study authors claim no GLP compliance is made for the results from the Mineralogical Analysis by X-Ray Diffraction (XRD).
****** The following deviations from the OECD TG 412 (2018) (28-day inhalation toxicity study) are noted:

- Exposure duration was 14 days.
- Haematology and clinical chemistry analyses were not performed.

Materials and methods

The 14-day inhalation toxicity study in rats aimed at identifying any adverse effects after short-term exposure to kaolin dust and at setting a NOAEC. Han Wistar rats of both sexes (5 rats/group/sex) were

exposed snout-only to Kaolin and Kaolinitic Clay at 25, 50 and 110 µg test item/L or air as negative control for 2 weeks (6 hours daily exposure, 5 days per week).

Animals were randomly allocated on arrival and each sex was allocated separately. Acclimatization period of at least 11 days preceded treatment. During the acclimatization period, observations of the animals and their cages were recorded at least once per day. In addition, the animals were acclimated to the method of restraint over at least a 3-day period preceding the first test item exposure.

The test items, Kaolin and Kaolinitic Clay, were administered by snout-only inhalation. Throughout the exposure, the animals were observed for mortality, signs of gross toxicity and behavioural changes at least twice per day. Physical exanimation took place once each week and signs of ill-health and incidences of lethality were recorded. Body weights, food and water consumption were monitored daily from day -5. In addition, samples of the test items were taken from the inhalation chambers for X-Ray diffraction (XRD) analysis. At the end of the observation period all animals were subjected to gross necropsy. No recovery period was included in the study design.

The study design was as follows:

Group	Treatment	Target exposure level (µg/L) #	Number of animals	
			males	females
1	Air control	0	5	5
2	Kaolin	25	5	5
3	Kaolin	50	5	5
4	Kaolin	110	5	5
5	Kaolinitic clay	25	5	5
6	Kaolinitic clay	50	5	5
7	Kaolinitic clay	110	5	5

Expressed in terms of test item as supplied.

During the terminal investigation, organ and body weight values were recorded. The left lung was processed for histological exanimation while the right lung was used for bronchoalveolar lavage (BAL) sampling. BAL fluid (BALF) was analysed in order to evaluate total and differential cell count (neutrophils, eosinophils, monocytes, macrophages and lymphocytes) and clinical chemistry parameters such as total protein, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), N-acetyl-β-D-glucosaminidase (U-NAG) and γ-glutamyl transferase (gGT).

Results

Atmosphere Analysis

The achieved concentrations for both test items were within 10% of the target concentration and the Mass Median Aerodynamic Diameters (MMAD) for all groups were within the required range of 1-3 µm for a repeat dose inhalation study.

Table B.6.3.3-1: Concentration of test items and Mass Median Aerodynamic Diameters (MMAD) of particles evaluated by X-Ray diffraction (XRD) analysis.

Group *	Test Item	Concentration (µg/L)		Mean achieved aerosol concentrations of target (%)	Particle size	
		Target	Achieved		MMAD (µm)	GSD
2	Kaolin	25	25.6	102	2.2	1.98
3	Kaolin	50	47.6	95	1.9	1.81
4	Kaolin	110	103	94	2.3	1.90
5	Kaolinitic Clay	25	23.7	95	1.6	2.10
6	Kaolinitic Clay	50	55.0	110	1.7	2.18
7	Kaolinitic Clay	110	103	94	1.8	2.25

* Group 1 was the control; GSD: Geometric standard deviation

Clinical observations

Clinical signs including abnormal gait (elevated/swaying) and hunched/flattened posture were observed in animals of all treatment groups on return to home cage. For males exposed to 25.6 or 47.6 µg/L Kaolin or 23.7 or 55.0 µg/L Kaolinitic Clay signs were typically seen only during Week 2. For males exposed to 103 µg/L Kaolin or Kaolinitic Clay and treated females clinical signs were seen throughout both weeks. On occasion, for females exposed to Kaolin at all concentrations and males exposed to 103 µg/L Kaolin and both sexes exposed to 55.0 or 103 µg/L Kaolinitic Clay, signs remained evident at the end of each day. All rats had returned to normal clinical condition prior to the next day's exposure and there were no signs on days without exposures (Day 6-7, 13-14).

Other signs associated with exposure included wet fur and red staining (head or eyes), on return to the home cage, on occasion in animals of all groups (including control). These signs were considered to be due to the method of restraint used and were not test item related.

Regarding body weight gains in males, values were similar to controls. In females, body weight gains were increased by 206%, 204% and 155% compared to controls for animals exposed to 25.6, 47.6 or 103 µg/L Kaolin, respectively. Accordingly, for females exposed to 23.7, 55.0 or 103 µg/L Kaolinitic Clay, body weights increased by 226%, 186% and 146% compared to controls. Since values lacked a concentration-response relationship, the study author attributed these differences to normal biological variation.

Table B.6.3.3-2: Mean body weight and body weight gain values in males[§]

Test Item	Concentration (µg/L)	Body weight, BW – group mean values (g)			BW gain (g) (% control)
		Day 1	Day 7	Day 15	Day 1-15
Control	0	240 ± 4.2	249 ± 8.1	269 ± 10.7	28 ± 6.6 (-)
Kaolin	25.6	233 ± 9.7	242 ± 11.9	260 ± 14.1	26 ± 5.5 (93%)
	47.6	236 ± 10.4	242 ± 11.2	262 ± 19.9	25 ± 11.0 (89%)
	103	239 ± 11.3	249 ± 18.4	264 ± 20.7	26 ± 11.7 (90%)
Kaolinitic Clay	23.7	227 ± 9.1	230 ± 11.5	250 ± 14.6	23 ± 6.4 (82%)
	55.0	236 ± 9.7	246 ± 11.3	270 ± 16.2	33 ± 9.7 (118%)
	103	240 ± 9.7	247 ± 12.7	266 ± 14.4	27 ± 6.3 (94%)

[§] N = 5 males per concentration group

Table B.6.3.3-3: Mean body weight and body weight gain values in females[§]

Test Item	Concentration (µg/L)	Body weight, BW – group mean values (g)			BW gain (g) (% control)
		Day 1	Day 7	Day 15	Day 1-15
Control	0	174 ± 7.3	174 ± 4.4	181 ± 5.7	7 ± 5.1 (-)
Kaolin	25.6	180 ± 7.3	180 ± 6.8	194 ± 7.9	14 ± 4.1 (206%)
	47.6	171 ± 2.4	177 ± 5.0	185 ± 5.3	14 ± 6.9 (204%)

Test Item	Concentration (µg/L)	Body weight, BW – group mean values (g)			BW gain (g) (% control)
		Day 1	Day 7	Day 15	Day 1-15
	103	168 ± 6.2	172 ± 7.9	179 ± 7.7	11 ± 4.8 (155%)
Kaolinitic Clay	23.7	176 ± 16.3	179 ± 17.1	192 ± 14.9	16 ± 9.0 (226%)
	55.0	174 ± 8.3	175 ± 11.2	187 ± 13.5	13 ± 7.1 (186%)
	103	171 ± 5.6	174 ± 5.5	181 ± 12.0	10 ± 12.2 (146%)

§ N = 5 females per concentration group

Food consumption followed a general pattern of lower consumption on exposure days and higher consumption on non-exposure days. Similar to body weight gains, any differences lacked concentration-response relationship and were therefore considered not to be test item related.

The adjusted weight of lungs/bronchi and spleen was statistically significantly increased among females treated with 103 µg/L kaolinitic clay. A similar observation was not made for animals treated with kaolin. Organ weights of kaolin treated animals were similar to controls. The increase in spleen weight (absolute and adjusted for terminal body weight) of all females treated with kaolin did not follow a concentration-response relationship and was not attributed to treatment.

Table B.6.3.3-4: Mean absolute and adjusted[#] organ weight values in males[§]

Test Item	Conc. (µg/L)	Terminal body weight (g)	Mean organ weight (adjusted mean) values (g)						
			Brain	Heart	Kidneys	Liver	Lungs & Bronchi	Spleen	Testes
Control	0	268 ± 10.4	1.835 ± 0.096 (1.819)	0.978 ± 0.159 (0.948)	1.647 ± 0.149 (1.601)	9.797 ± 0.751 (9.442)	1.122 ± 0.113 (1.106)	0.623 ± 0.084 (0.614)	3.191 ± 0.146 (3.131)
Kaolin	25.6	257.5 ± 14.5	1.868 ± 0.100 (1.879)	0.942 ± 0.128 (0.964)	1.619 ± 0.135 (1.652)	9.721 ± 0.847 (9.973)	1.180 ± 0.079 (1.192)	0.614 ± 0.075 (0.620)	2.986 ± 0.253 (3.030)
	47.6	260.3 ± 19.6	1.930 ± 0.043 (1.934)	0.934 ± 0.100 (0.942)	1.711 ± 0.207 (1.724)	10.302 ± 1.745 (10.394)	1.208 ± 0.084 (1.212)	0.580 ± 0.062 (0.583)	3.083 ± 0.202 (3.099)
	103	263.3 ± 20.9	1.877 ± 0.078 (1.874)	0.855 ± 0.030 (0.848)	1.581 ± 0.145 (1.571)	9.709 ± 0.562 (9.633)	1.183 ± 0.062 (1.179)	0.613 ± 0.059 (0.611)	3.202 ± 0.377 (3.189)
Kaolinitic Clay	23.7	249.6 ± 14.6	1.834 ± 0.073 (1.865)	0.865 ± 0.102 (0.926)	1.507 ± 0.154 (1.600)	9.635 ± 1.115 (10.341)	1.131 ± 0.079 (1.164)	0.576 ± 0.052 (0.594)	2.988 ± 0.252 (3.110)
	55.0	268.8 ± 14.9	1.889 ± 0.106 (1.871)	1.040 ± 0.163 (1.007)	1.638 ± 0.143 (1.586)	10.485 ± 1.217 (10.090)	1.279 ± 0.118 (1.261)	0.718 ± 0.051 (0.707)	3.097 ± 0.471 (3.029)
	103	265.9 ± 13.4	1.879 ± 0.052 (1.869)	0.949 ± 0.151 (0.930)	1.647 ± 0.111 (1.618)	10.446 ± 1.142 (10.220)	1.147 ± 0.033 (1.137)	0.597 ± 0.094 (0.591)	3.315 ± 0.149 (3.276)

[§] N = 5 males per concentration group

For organ weight data, analysis of covariance was performed using terminal body weight as covariate (Angervall and Carlstrom 1963), unless non-parametric methods were applied. The treatment comparisons were made on adjusted group means in order to allow for differences in body weight which might influence the organ weights.

Table B.6.3.3-5: Mean absolute and adjusted[#] organ weight values in females[§]

Test Item	Conc. (µg/L)	Terminal body weight (g)	Mean organ weight (adjusted mean) values (g)					
			Brain	Heart	Kidneys	Liver	Lungs & Bronchi	Spleen
Control	0	181.2 ± 5.4	1.743 ± 0.043	0.735 ± 0.100 (0.748)	1.164 ± 0.102 (1.191)	7.042 ± 0.748 (7.253)	0.919 ± 0.028 (0.940)	0.387 ± 0.037 (0.406)
Kaolin	25.6	196.9 ± 7.6	1.817 ± 0.065	0.853 ± 0.151 (0.828)	1.263 ± 0.064 (1.212)	7.673 ± 0.619 (7.269)	0.970 ± 0.038 (0.932)	0.513 ± 0.041 (0.479)
	47.6	185.7 ± 6.4	1.762 ± 0.026	0.776 ± 0.055 (0.778)	1.203 ± 0.086 (1.208)	6.970 ± 0.308 (7.007)	0.921 ± 0.064 (0.926)	0.500 ± 0.109 (0.503)
	103	178.0 ± 7.1	1.775 ± 0.045	0.731 ± 0.151 (0.752)	1.165 ± 0.115 (1.208)	7.116 ± 0.755 (7.452)	0.933 ± 0.062 (0.967)	0.438 ± 0.083 (0.467)
Kaolinitic	23.7	194.4 ±16.2	1.721 ± 0.062	0.790 ± 0.139	1.234 ± 0.063	7.633 ± 0.819	0.998 ± 0.064	0.522 ± 0.076

Test Item	Conc. (µg/L)	Terminal body weight (g)	Mean organ weight (adjusted mean) values (g)					
			Brain	Heart	Kidneys	Liver	Lungs & Bronchi	Spleen
Clay				(0.771)	(1.196)	(7.329)	(0.970)	(0.496)
	55.0	189.1 ± 14.3	1.539 ± 0.312	0.788 ± 0.076 (0.782)	1.219 ± 0.199 (1.207)	7.437 ± 0.603 (7.340)	0.984 ± 0.093 (0.964)	0.477 ± 0.077 (0.468)
	103	181.0 ± 12.5	1.742 ± 0.057	0.795 ± 0.133 (0.808)	1.171 ± 0.044 (1.199)	7.362 ± 0.411 (7.582)	1.025 ± 0.079 (1.048**)	0.481 ± 0.059 (0.500*)

§ N = 5 females per concentration group

For organ weight data, analysis of covariance was performed using terminal body weight as covariate (Angervall and Carlstrom 1963), unless non-parametric methods were applied. The treatment comparisons were made on adjusted group means in order to allow for differences in body weight which might influence the organ weights.

* $p<0.05$ (for comparisons with control group)

** $p<0.01$ (for comparisons with control group)

Bronchoalveolar Lavage (BAL) analysis - Supernatant

Mean total protein (Prot), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), N-Acetyl-β-D-Glucosaminidase (U-NAG) and gamma glutamyl transferase (gGT) concentrations were typically higher for all treated groups when compared to controls, with the exception of total protein and LDH for females which were generally lower than control values. The individual data for animals exposed to Kaolin or Kaolinitic Clay were typically within the range of the control data, for the sexes combined, and therefore any differences from control in the mean data were of questionable toxicological significance.

Table B.6.3.3-6: Bronchoalveolar Lavage (BAL) data – group mean values at termination in males[§]

Test Item	Conc. (µg/L)	Bronchoalveolar Lavage Group Mean Data				
		Prot (g/L)	ALP (U/L)	LDH (U/L)	U_NAG (U/L)	gGT (U/L)
Control	0	0.11 ± 0.034	69 ± 7.5	119 ± 30.7	7.5 ±2.22	7 ± 1.5
Kaolin	25.6	0.71 ± 0.860	127 ± 41.6**	566 ± 256.4**	7.5 ±3.17	10 ± 2.3*
	47.6	0.44 ± 0.510	118 ± 51.6**	405 ± 234.7**	9.3 ±2.45	12 ± 6.1**
	103	0.15 ± 0.055	111 ± 32.7**	231 ± 104.6	10.9 ±7.94	14 ± 3.0*
Kaolinitic Clay	23.7	0.12 ± 0.030	96 ± 5.1	153 ± 51.8	3.3 ± 1.21**	9 ±0.7
	55.0	0.24 ± 0.173	115 ± 30.6	261 ± 153.2	7.0 ± 3.17	11 ± 3.0**
	103	0.13 ± 0.025	84 ± 17.6	156 ± 33.0	9.5 ± 1.22	10 ± 1.9

§ N = 5 males per concentration group
* p<0.05 (for comparisons with control group)
** p<0.01 (for comparisons with control group)

Table B.6.3.3-7: Bronchoalveolar Lavage (BAL) data – group mean values at termination in females[§]

Test Item	Conc. (µg/L)	Bronchoalveolar Lavage Group Mean Data				
		Prot (g/L)	ALP (U/L)	LDH (U/L)	U_NAG (U/L)	gGT (U/L)
Control	0	0.51 ± 0.574	67 ± 15.2	338 ± 308.9	7.5 ± 2.91	7 ± 2.4
Kaolin	25.6	0.28 ± 0.239	80 ± 35.4	300 ± 165.1	7.5 ± 2.93	8 ± 4.5
	47.6	0.21 ± 0.204	100 ± 22.1	256 ± 88.7	7.3 ± 3.02	11 ± 4.2
	103	0.30 ± 0.378	82 ± 26.1	347 ± 390.7	7.1 ± 2.72	13 ± 3.1*
Kaolinitic Clay	23.7	0.20 ± 0.210	68 ± 19.4	236 ± 102.4	10.9 ± 4.10	10 ± 2.6
	55.0	0.25 ± 0.365	103 ± 27.8	318 ± 335.5	6.8 ± 2.84	8 ± 2.2
	103	0.16 ± 0.058	90 ± 25.0	274 ± 92.9	10.3 ± 2.86	15 ± 3.0**

§ N = 5 females per concentration group
* p<0.05 (for comparisons with control group)
** p<0.01 (for comparisons with control group)

Bronchoalveolar Lavage (BAL) analysis – Cell pellet

In male rats treated with kaolin, there were statistically significant decreases in mononuclear cell counts as percentages of total white blood cells with concomitant increases in neutrophil and lymphocyte counts. Moreover, eosinophil counts were significantly increased among males of all groups treated with kaolinitic clay and females treated with 103 µg/L of the same compound. Although statistically significant, changes in differential cell counts were considered of unclear toxicological importance. There are no historical control data to further assess biological relevance.

There were no other test item related differences in total and differential cell count (neutrophils, eosinophils, monocytes and macrophages and lymphocytes) between treated and control animals of either sex.

Table B.6.3.3-8: Bronchoalveolar Lavage (BAL) – group mean differential cell counts in the right lung in males

Test Item	Conc. (µg/L)	Different cell counts calculated per animal (10^6/animal)				
		Total Cells	Neutrophils	Eosinophils	Mononuclear cells	Lymphocytes
Control	0	1.73 ± 0.43	0.06 ± 0.02	0.00 ± 0.00	1.62 ± 0.43	0.05 ± 0.04
Kaolin	25.6	3.71 ± 2.29	0.60 ± 0.50*	0.09 ± 0.08	2.43 ± 097	0.59 ± 0.95
	47.6	2.79 ± 0.95	0.30 ± 0.19*	0.04 ± 0.04	1.99 ± 0.56	0.45 ± 0.52*
	103	2.28 ± 1.3	0.28 ± 0.33	0.05 ± 0.05	1.80 ± 0.89	0.14 ± 0.07*
Kaolinitic Clay	23.7	2.07 ± 1.44	0.25 ± 0.40	0.07 ± 0.06	1.67 ± 1.07	0.08 ± 0.05
	55.0	2.01 ± 0.82	0.10 ± 0.11	0.07 ± 0.04	1.73 ± 0.80	0.11 ± 0.04
	103	1.58 ± 0.33	0.11 ± 0.02	0.02 ± 0.03	1.40 ± 0.35	0.05 ± 0.0
Test Item	**Conc. (µg/L)**	**Differential cell counts as a percentage of total white blood cells (%)**				
		Neutrophils	**Eosinophils**	**Mononuclear cells**	**Lymphocytes**	
Control	0	3.62 ±1.32	0.00 ± 0.00	93.28 ± 2.92	3.10 ±2.37	
Kaolin	25.6	13.62 ± 8.78*	2.24 ± 1.58	73.10 ± 17.91*	10.36 ± 12.40	
	47.6	10.04 ± 3.87*	1.36 ± 1.40	73.68 ± 15.24*	14.36 ± 12.21*	
	103	10.3 ± 5.84*	1.98 ± 2.04	80.50 ± 7.56*	6.52 ± 1.62*	
Kaolinitic Clay	23.7	9.54 ± 8.02	3.60 ± 2.77*	82.20 ± 8.63	4.42 ± 1.43	
	55.0	5.54 ± 5.56	4.10 ± 2.82*	84.70 ± 7.05	5.66 ± 1.25	
	103	7.18 ± 2.00	1.52 ± 2.59*	88.04 ± 3.72	3.26 ± 0.61	

§ N = 5 males per concentration group

* p<0.05 (for comparisons with control group)

Table B.6.3.3-9: Bronchoalveolar Lavage (BAL) – group mean differential cell counts in the right lung in females

Test Item	Conc. (µg/L)	Different cell counts calculated per animal (10^6/animal)				
		Total Cells	Neutrophils	Eosinophils	Mononuclear cells	Lymphocytes
Control	0	3.26 ± 1.88	0.46 ± 0.41	0.07 ± 0.07	2.49 ± 1.38	0.24 ± .17
Kaolin	25.6	1.55 ± 0.63	0.21 ± 0.18	0.03 ± 0.04	1.15 ± 0.41	0.16 ± 0.18
	47.6	1.63 ± 0.65	0.11 ± 0.10	0.02 ± 0.03	1.39 ± 0.48	0.11 ± 0.10
	103	2.72 ± 2.15	0.38 ± 0.44	0.08 ± 0.06	1.85 ± 1.11	0.40 ± 0.63
Kaolinitic Clay	23.7	1.98 ± 0.21	0.20 ± 0.08	0.04 ± 0.04	1.53 ± 0.21	0.21 ± 0.14
	55.0	2.11 ± 0.66	0.22 ± 0.16	0.05 ± 0.00	1.72 ± 0.41	0.12 ± 0.11
	103	2.65 ± 1.40	0.49 ± 0.43	0.12 ± 0.07	1.89 ± 1.16	0.14 ± 0.13
Test Item	**Conc. (µg/L)**	**Differential cell counts as a percentage of total white blood cells (%)**				
		Neutrophils	**Eosinophils**	**Mononuclear cells**	**Lymphocytes**	
Control	0	10.96 ± 8.12	1.58 ± 1.48	78.48 ± 12.08	8.08 ± 4.36	
Kaolin	25.6	11.36 ± 8.60	1.52 ± 2.37	77.60 ± 17.57	9.08 ± 9.70	
	47.6	5.90 ± 3.83	1.30 ± 1.93	86.64 ±6.13	6.16 ± 4.39	
	103	10.74 ±7.05	3.22 ± 2.40	76.32 ± 15.06	9.20 ± 9.30	
Kaolinitic Clay	23.7	10.22 ± 4.69	2.20 ± 2.36	76.96 ± 8.49	10.24 ± 5.53	
	55.0	9.40 ±4.57	2.54 ± 0.78	83.22 ± 7.76	4.84 ± 4.55	
	103	17.54 ± 10.72	4.70 ± 2.24*	72.30 ± 14.31	5.16 ± 3.18	

§ N = 5 females per concentration group

* p<0.05 (for comparisons with control group)

Macropathology

The macroscopic examination performed after 2 weeks of exposure revealed no test item-related lesions.

Histopathology

Minimal alveolar macrophage aggregates were seen in the lungs of animals exposed to Kaolin, or Kaolinitic Clay. The alveolar macrophage aggregates contained fine refractile granular material which was considered likely to be the test item. According to the study author any differences in the incidences of this finding between treated groups were considered to be incidental and likely linked to the pattern of distribution of alveolar macrophages in individual animals when fixative was instilled into the lungs at necropsy. There was no clear concentration response relationship and no associated degenerative changes.

Table B.6.3.3-10: Incidences of alveolar macrophage aggregates in the lungs of male animals killed after 2 weeks of treatment

		Air	Kaolin			Kaolinitic Clay		
Achieved concentration (µg/L)		0	25.6	47.6	103	27.3	55.0	103
Alveolar macrophage aggregates	**minimal**	0	1	4	3	2	4	1
	total	0	1	4	3	2	4	1
Number of tissues examined		5	5	5	5	5	5	5

Table B.6.3.3-11: Incidences of alveolar macrophage aggregates in the lungs of female animals killed after 2 weeks of treatment

		Air	Kaolin			Kaolinitic Clay		
Achieved concentration (µg/L)		0	25.6	47.6	103	27.3	55.0	103
Alveolar macrophage aggregates	**minimal**	0	2	3	2	2	5	5
	total	0	2	3	2	2	5	5
Number of tissues examined		5	5	5	5	5	5	5

Mucous cell hyperplasia/metaplasia was observed in the nose of animals exposed to the highest dose of Kaolin or Kaolinitic Clay. It was mainly localized to the ventral respiratory epithelium in the caudal aspect of the nose. Thus, it was considered a local effect, secondary to mild irritation caused by the test items.

Table B.6.3.3-12: Incidences of mucous cell hyperplasia/metaplasia in the nose of male animals killed after 2 weeks of treatment

		Air	Kaolin			Kaolinitic Clay		
Achieved concentration (µg/L)		0	25.6	47.6	103	27.3	55.0	103
Hyperplasia/Metaplasia, Mucous Cell	**minimal**	0	-	-	3	-	-	2
	slight	0	-	-	2	-	-	1
	total	0	-	-	5	-	-	3
Number of tissues examined		5	-	-	5	-	-	5

Table B.6.3.3-13: Incidences of mucous cell hyperplasia/metaplasia in the nose of female animals killed after 2 weeks of treatment

		Air	Kaolin			Kaolinitic Clay		
Achieved concentration (µg/L)		0	25.6	47.6	103	27.3	55.0	103
Hyperplasia/Metaplasia, Mucous Cell	**minimal**	0	-	-	1	-	-	3
	slight	0	-	-	3	-	-	2
	total	0	-	-	4	-	-	5

	Air	Kaolin			Kaolinitic Clay		
Number of tissues examined	5	-	-	5	-	-	5

Conclusion

A snout-only inhalation study in Han Wistar rats was performed for 6 hours a day, 5 days a week, for 2 weeks at achieved aerosol concentrations of 25.6, 47.6 or 103 µg/L Kaolin or 23.7, 55.0 or 103 µg/L Kaolinitic Clay.

Treatment-related observations included minimal alveolar macrophage aggregates in the lungs of animals exposed to Kaolin or Kaolinitic Clay at all concentrations tested. The alveolar macrophage aggregates contained fine refractile granular material which was considered by the study authors likely to be the test item. There was no other morphological change in the lung and there was no mention of inflammation in the study report. Considering the inert and insoluble properties of Kaolin and Kaolinitic clay, minimal alveolar macrophage aggregates could be regarded as adaptive responses to clear the lungs of foreign particulate matter. However, the study did not include a recovery period in order to assess reversibility of the finding.

Analyses of the bronchoalveolar lavage fluid (BALF) revealed statistically significant changes in differential white blood cell counts, with no clear concentration-response pattern. There were no historical control data to assess biological significance. The adjusted weight of lungs/bronchi was statistically significantly increased among females treated with 103 µg/L kaolinitic clay.

Overall, it cannot be clearly demonstrated that the observed lung effects (i.e. increased lung weight, accumulation of macrophages and changes in differential white blood cell counts in the BALF) are adaptive or adverse. It is likely that these findings are adaptive responses and parts of a defence mechanism aimed to clear the lungs of particulate matter and are therefore non-specific findings. On the other hand, the study is of short-duration (14-days) and there are no other studies on short-term or long-term toxicity of kaolin *via* the inhalation route to assess progression of the lung effects. Thus, progression into fibrosis with lung function changes after longer exposure may not be excluded considering that macrophages play a central role in the pathogenesis of fibrosis.

Other effects at site of contact included increased incidence of mucous cell hyperplasia/metaplasia in the nose of animals exposed to the highest dose of Kaolin or Kaolinitic Clay. This effect was mainly localized to the ventral respiratory epithelium in the caudal aspect of the nose and it was considered secondary to mild irritation caused by the test items.

In conclusion, the RMS is proposing to set the study NOAEC at 47.6 µg/L for kaolin and 55.0 µg/L for kaolinitic clay based on nasal turbinates effects (mucous cell hyperplasia/metaplasia) at 103 µg/L. This NOAEC is supported by lung effects (i.e changes in differential white blood cell counts, minimal alveolar macrophage aggregates, increased adjusted weight of lungs/bronchi) as a conservative approach, given the uncertainty raised due to short study duration and lack of reversibility period not allowing to assess potential progression to functional lung changes.

Summary and conclusions on short-term toxicity studies

No short-term oral toxicity data with aluminium silicate calcined have been provided to the RMS by either of the notifiers. In the REACH dossier for CAS No. 92704-41-1 no short-term toxicity data were available on Kaolin, calcined. The RMS considers that waiving of oral short-term toxicity studies is considered acceptable since aluminium silicate is a natural inorganic mineral, it is inert, insoluble in aqueous and organic solvents and it does not become bioavailable when ingested.

A snout-only inhalation study in Han Wistar rats was performed for 6 hours a day, 5 days a week, for 2 weeks at achieved aerosol concentrations of 25.6, 47.6 or 103 µg/L Kaolin or 23.7, 55.0 or 103 µg/L Kaolinitic Clay (nominal concentrations for both compounds: 25, 50 and 110 µg/L). The study NOAEC was set at 47.6 µg/L for kaolin and 55.0 µg/L for kaolinitic clay based on effects on nasal turbinates (mucous cell hyperplasia/metaplasia) at 103 µg/L. This NOAEC is supported by lung

effects including changes in differential white blood cell counts, minimal alveolar macrophage aggregates, increased adjusted weight of lungs/bronchi. Although lung effects were presumed to be adaptive, there is high uncertainty due to short study duration and lack of reversibility period not allowing to assess potential progression to functional lung changes. So, lung effects are considered in NOAEC setting as a conservative approach.

Table B.6.3-1: Summary of the short-term study with aluminium silicate

Species, Route, Duration	Test item(s)	Concentration	Endpoint	Reference
Rat (Han Wistar), Inhalation (snout only), 2-weeks	**Kaolin** (92,3% Kaolinite; 0,8% Quartz) **Kaolinitic clay** (75,3% Kaolinite; 17% Quartz)	*Nominal:* 0, 25, 50, 110 µg/L *Achieved:* **Kaolin:** 0, 25.6, 47.6 103 µg/L **Kaolinitic Clay:** 0, 23.7, 55.0, 103	NOAEC = 47.6 µg/L (kaolin) Effects at LOAEC = 103 µg/L: - Nasal turbinates effects (mucous cell hyperplasia/metaplasia) - Lung effects (changes in differential white blood cell counts, minimal alveolar macrophage aggregates, increased adjusted weight of lungs/bronchi) GLP study. No Guideline. **Study acceptable.**	[redacted], 2019 (Study submitted for the renewal)

The NOAEC of 47.6 µg/L set for kaolin after treatment *via* the inhalation route is used for AOEC setting for consideration in non-dietary risk assessment.

B.6.4 GENOTOXICITY (ANNEX IIA 5.4)

No genotoxicity study on Kaolin ~~is~~ was available in DAR (2008). The Notifier Tessenderlo Group N.V. had requested that a waiver for genotoxicity be granted for kaolin in view of its excellent safety record despite continuous use as a food additive, pharmaceutical ingredient, personal hygiene component and in many industrial applications.

In the frames of the active substance renewal, only the applicant SOKA submitted an *in vitro* bacterial mutagenicity assay (Wisher, 2017), which is described below (section B.6.4.1), whereas Tessenderlo Group N.V. provided again the same justification for waiving genotoxicity testing as it was included in the DAR.

B.6.4.1 *In vitro* studies

Previous evaluation:	None; submitted by SOKA for the purpose of the a.s. renewal

Reference:	**KCA 5.4.1-01 (Wisher M., 2017)**
Report No:	LF13TQ
Title	Kaolin: Reverse Mutation Assay 'Ames Test' using *Salmonella typhimurium* and *Escherichia coli*

Test substance/purity	Hydrous Kaolin (hydrous Aluminium silicate) / 100%
Lot/Batch no:	30.03.2015
Guideline:	OECD 471 (1997), Regulation (EC) No. 440/2008 method B.13/14, USA, EPA OCSPP harmonized guideline 870.5100
GLP:	Yes (certified laboratory)
Deviation:	1) Stability of Kaolin was not reported 2) ENNG was used as a positive control in TA100 and TA1535 cultures without S9 3) 4NQO was used as a positive control in TA98 cultures without S9
Reliability	Klimisch score 1 (Reliable)
Acceptability:	Yes.
Species/strain	*Salmonella typhimurium* (TA98, TA100, TA1535, TA1537) and *E. coli* WP2 (pKM101)

Test system:

Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100 and *Escherichia coli* strain WP2uvrA were treated with hydrous kaolin using both the Ames plate incorporation and pre-incubation methods up to eight concentrations, in triplicates, both with and without S9 liver metabolizing system (10%). The concentrations used for Experiment 1 (plate incorporation method) ranged from 1.5 to 5000 µg/plate. On a seperate day, Experiment 2 (pre-incubation method) was performed using six concentations ranging from 15 to 5000 µg/plate. Stability of Kaolin was not provided, unlike with OECD TG 471 (1997); instead the applicant stated that: "Analysis for concentration, homogeneity and stability of the test item formulations is not a requirement of the test guidelines and was, therefore, not determined. This is an exception with regard to GLP and has been reflected in the GLP compliance statement."

Results

There was no visible reduction in the growth of the bacterial background lawn at any dose level, either in the presence or absence of metabolic activation (S9-mix), in Experiment 1 (plate incorporation method). The same maximum dose level was used in Experiment 2 and there was a reduction in cultures of strain WP2uvra without S9 at concentrations of 1500 µg/plate and above; and also in cultures of TA98 with S9 at 5000 µg/plate. No other visible reduction in the growth of the bacterial background lawn with or without S9 was observed in Experiment 2. A creamy test item film with an associated particulate precipitate was noted at 5000 µg/plate both in Experiment 1 and 2 with and without S9. This observation did not prevent the scoring of revertant colonies. There were no increases in the frequency of revertant colonies recorded for any of the bacterial strains, with any dose of the test item, either with or without metabolic activation (S9-mix), in Experiments 1 and 2. The results are presented in tables B.6.4.1-1 and B.6.4.1-2. The vehicle (dimethyl sulphoxide) control plates gave counts of revertant colonies within the normal range and that of negative historical control data (Table B.6.4.1-3). Concerning positive controls, N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG) was used in cultures of TA100, TA1535 and WP2uvrA without S9, although the strain-specific positive control recommended by the OECD TG 471 (1997) for TA100 and TA1535 is sodum azide. Similarly, 4-Nitroquinoline-1-oxide (4NQO) was used in TA98 cultures without S9, instead of 2-nitrofluorene. However, all positive controls seemed to respond properly and marked increases in the frequency of revertant colonies were observed both with and without metabolic activation. Thus, the sensitivity of the assay and the efficacy of the S9-mix were validated. The historical positive control data are presented in table B.6.4.1-4.

Table B.6.4.1-1: Test results of Experiment 1 (plate incorporation method)

Test item	Concentration (µg/plate)	Mean number of revertants +/- SD				
		Base-par substitution type			Frameshift type	
		TA100	TA1535	WP2*uvrA*	TA98	TA1537
Without metabolic activation (- S9 mix)						
Solvent control (DMSO)		77 / 4.6	17 / 12.5	25 / 4.6	23 / 5.6	11 / 3.2
Kaolin	1.5	76 / 9.5	15 / 11.0	22 / 4.2	16 / 1.5	10 / 1.2
	5	72 / 4.0	16 / 1.0	26 / 6.0	26 / 3.0	11 / 6.8
	15	68 / 5.6	10 / 2.6	21 /6.4	21 / 5.9	16 /2.6
	50	70 / 4.6	17 / 2.9	27 / 6.0	22 / 3.6	11 / 6.1
	150	73 /7.0	13 / 2.3	29 / 4.7	17 / 3.2	15 / 5.3
	500	79 / 12.3	12 / 3.8	26 / 5.5	24 / 1.2	13 / 0.0
	1500	79 /8.5	10 / 1.7	27 / 3.0	22 / 7.1	13 / 6.0
	5000	76 / 4.6 PF	13 / 2.3 PF	26 / 8.3 PF	23 / 9.0 PF	10 / 1.5 PF
Positive controls	Name	ENNG	ENNG	ENNG	4NQO	9AA
	Concentration (µg/plate)	3	5	2	0.2	80
	No. of revertants	552 / 4.9	320 / 72.9	740 / 51.9	248 / 13.9	273 / 62.5
With metabolic activation (+ S9 mix)						
Solvent control (DMSO)		92 / 5.3	12 /4.4	23 / 5.2	19 / 10.1	10 / 4.2
Kaolin	1.5	89 / 4.6	12 / 6.4	26 / 3.2	24 / 3.2	9 / 3.5
	5	89 / 6.1	16 / 8.1	25 / 1.7	28 / 8.9	8 / 5.6
	15	87 / 8.9	13 / 1.5	32 / 7.8	20 / 9.0	10 / 4.7
	50	89 / 22.6	11 / 4.7	27 / 3.1	20 / 1.7	8 / 5.3
	150	90 / 12.3	12 / 3.5	28 / 4.0	19 / 6.1	8 / 3.5
	500	94 / 10.2	12 / 0.6	31 / 5.7	22 / 7.2	9 / 2.0
	1500	86 / 8.7	13 / 3.1	28 / 6.0	27 / 2.5	9 / 4.4
	5000	81 / 10.1 PF	12 / 1.2 PF	27 / 12.1 PF	19 / 8.6 PF	10/ 0.6 PF
Positive controls	Name	ENNG	ENNG	ENNG	4NQO	9AA
	Concentration (µg/plate)	3	5	2	0.2	80
	No. of revertants	1297 / 402.1	199 / 21.7	262 / 9.6	199 / 13.6	426 / 29.4

P: test item precipitation; F: test item film
ENNG: N-ethyl-N'-nitro-N-nitrosoguanidine; 4NQO: 4-Nitroquinoline-1-oxide; 9AA: 9-Aminoacridine

Table B.6.4.1-2: Test results of Experiment 2 (pre-incubation method)

Test item	Concentration (µg/plate)	Mean number of revertants / SD				
		Base-par substitution type			Frameshift type	
		TA100	TA1535	WP2*uvrA*	TA98	TA1537
Without metabolic activation (- S9 mix)						
Solvent control (DMSO)		80 / 1.2	16 / 6.0	28 / 7.6	15 / 4.2	12 / 4.0
Kaolin	15 µg	77 / 11.5	16 / 5.1	30 / 8.1	17 / 10.4	9 / 1.7
	50 µg	80 / 6.2	17 / 2.9	28 / 6.1	17 / 2.1	4 / 5.0
	150 µg	81 / 8.3	17 / 3.8	25 / 5.6	12 / 4.4	12 / 2.1
	500 µg	78 / 12.3	9 / 1.5	24 / 4.0	18 / 4.7	14 / 7.6
	1500 µg	86 / 9.3	12 / 1.2	19 / 2.1	15 / 1.7	12 / 7.0
	5000 µg	89 / 5.1 PF	10 / 3.1 PF	12 / 1.0 PF	12 / 5.0 PF	9 / 0.6 PF
Positive	Name	ENNG	ENNG	ENNG	4NQO	9AA

controls	Concentration (µg/plate)	3	5	2	0.2	80
	No. of revertants	474 / 113.4	331 / 83.4	375 / 15.7	246 / 5.1	143 / 30.0
With metabolic activation (+ S9 mix)						
Kaolin	**Concentration (µg/plate)**	**TA100**	**TA1535**	**WP2*uvrA***	**TA98**	**TA1537**
	Solvent control (DMSO)	84 / 11.5	19 / 4.7	30 / 6.7	24 / 5.9	11 / 5.0
	15 µg	93 / 11.5	19 / 2.1	29 / 2.0	21 / 6.0	12 / 2.9
	50 µg	90 / 10.3	24 / 4.6	31 / 1.7	21 / 3.0	12 / 2.9
	150 µg	78 / 6.1	17 / 0.6	24 / 3.8	19 / 6.7	6 / 3.1
	500 µg	84 / 1.7	15 / 7.1	29 / 3.6	18 / 3.8	13 / 4.2
	1500 µg	94 / 11.6	9 / 2.9	27 / 2.6	18 / 2.0	8 / 2.5
	5000 µg	87 / 14.5 PF	16 / 0.6 PF	26 / 0.6 PF	10 / 2.5 PF	8 / 5.8 PF
Positive controls	Name	ENNG	ENNG	ENNG	4NQO	9AA
	Concentration (µg/plate)	3	5	2	0.2	80
	No. of revertants	864 / 166.9	177 / 6.0	159 / 29.8	108 / 19.7	159 / 10.2

P: test item precipitation; F: test item film
ENNG: N-ethyl-N'-nitro-N-nitrosoguanidine; 4NQO: 4-Nitroquinoline-1-oxide; 9AA: 9-Aminoacridine

Table B.6.4.1-3: Historical control data – Vehicle and untreated control values

2015																
Strain	**TA100**		**TA1535**		**TA102**		**WP2uvrA**		**TA98**		**TA1537**		**WP2uvrA pKM101**		**pKM101**	
S9-mix	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Values*	274	278	504	285	26	13	461	229	526	299	506	282	42	51	39	49
Min	60	61	7	7	222	278	10	12	11	10	4	6	87	98	89	93
Max	166	175	31	29	376	388	58	43	45	46	27	27	237	254	174	177
Mean	91	95	16	14	286	333	24	27	21	24	12	13	156	164	123	137
Sd	19.3	19.1	4.5	4.0	48.7	37.6	5.6	5.9	6.2	6.1	3.8	3.4	42.2	35.6	23.1	21.2
2016																
Values*	399	401	758	393	60	30	690	345	788	415	762	398	32	32	16	24
Min	63	66	8	8	216	221	10	13	8	12	3	4	97	104	78	52
Max	154	156	34	39	340	375	53	53	49	51	24	23	268	243	148	166
Mean	90	93	15	15	268	310	22	27	21	25	12	13	161	159	118	110
Sd	14.5	14.3	4.5	5.2	26.4	31.1	5.8	6.3	4.8	5.7	3.5	3.5	39.2	32.3	17.0	29.3

*number of mean values used to create dataset; SD: standard deviation; Min: minimum value; Max: maximum value

Table B.6.4.1-4: Historical control data – Positive control values

2015																
Strain	**TA100**		**TA1535**		**TA102**		**WP2uvrA**		**TA98**		**TA1537**		**WP2uvrA pKM101**		**pKM101**	
S9-mix	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
Values*	276	280	252	264	13	13	231	227	262	276	253	261	20	35	20	35
Min	222	250	79	118	953	673	116	103	100	78	164	97	430	494	745	325
Max	2266	2402	2779	457	3140	1655	2769	550	502	705	2318	823	1696	2264	3662	1174
Mean	614	927	472	246	2303	1093	792	266	222	218	911	336	761	1461	2257	569
Sd	260.6	452.5	434.8	55.7	815.2	376.5	342.1	97.7	70.2	107.6	412.4	135.7	350.0	382.0	790.7	220.3
2016																

Values*	409	406	381	386	30	28	341	335	388	385	379	381	14	24	8	16
Min	221	284	84	92	897	629	107	102	100	96	95	101	445	574	1674	372
Max	2222	2863	2994	879	2326	2140	1611	637	449	4357	1413	639	1117	1855	2823	945
Mean	724	1264	854	240	1633	950	718	240	186	188	406	290	743	1271	2379	535
Sd	320.4	562.9	664.9	62.1	564.5	382.7	338.6	98.2	49.8	230.8	227.0	92.7	214.6	326.5	426.2	143.3

*number of mean values used to create dataset; SD: standard deviation; Min: minimum value; Max: maximum value

Conclusions:

Aluminium Silicate (Kaolin) was considered to be non-mutagenic under the conditions tested, in strains *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537) and *E. coli* WP2 (pKM101) at concentrations up to 5000 µg/plate with and without S9 metabolic activation.

B.6.4.2 *In vivo* studies in somatic cells

The applicant SOKA provided no *in vivo* studies based on the following justification:
"Aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not become bioavailable when ingested. Aluminium silicate has been, and still is used, extensively as an ingredient in anti-diarrhoeal medication. In Europe, Aluminium silicate is approved for use as an anti-caking agent in feed and has the feed additive number E559 for all animals feedingstuffs and all species or categories with no maximum concentration. Aluminium silicate is also listed in the internationally recognized Food Chemical Codex as a food additive. In view of the inert nature of Aluminium silicate, its natural occurrence, extremely low toxicity and chronic exposure in everyday life through medicines, toiletries and natural environment no genotoxicity study is required."

B.6.4.3 *In vivo* studies in germ cells

There are no *in vivo* genotoxicity studies in germ cells available and they are not required considering the inert nature of Aluminium silicate, its natural occurrence and chronic exposure in everyday life through medicines and toiletries.

Summary of genotoxicity studies

There are no genotoxicity data with Aluminium silicate calcined. Hydrous Kaolin was negative in a bacterial mutagenicity assay submitted by SOKA (Wisher, 2017).

Table B.6.4-1: Summary of the *in vitro* genotoxicity study with aluminium silicate

Test / endpoint	Test system	Findings	Result	Reference
Bacterial mutagenicity	Ames test *Salmonella* strains TA98, TA100, TA1535, TA1537 *E. coli* WP2 (pKM101)	Not mutagenic +/- metabolic activation up to 5000 µg/plate	Negative	Wisher, 2017 (Study submitted for the renewal)

The RMS considers that waiving of genotoxicity data may be acceptable considering that aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents and it does not become bioavailable when ingested.

A similar approach has been described in the RAR (2019) for Kieselgur (diatomaceous earth), another silica compound, where no *in vitro* studies were evaluated, as the potential of kieselgur to induce genotoxicity was considered irrelevant. Considering *in vivo* data, the results from a Comet assay with Diatomaceous earth did not reveal any genotoxic potential. This approach is further supported considering literature data included in the RAR for Kieselgur (diatomaceous earth), where it is noted that genotoxic effects in alveolar epithelial cells occurred only after crystalline but not amorphous silica exposure (Johnston *et al.*, 2000).

No relevant genotoxicity data on calcined Kaolin were retrieved from the systematic literature search performed by both applicants.

B.6.5 LONG-TERM TOXICITY AND CARCINOGENICITY (ANNEX IIA 5.5)

No GLP and/or guideline complying long term-carcinogenicity study on Aluminium Silicate is available.

The Notifier Tessenderlo Group N.V. requested that a waiver for long term and carcinogenicity studies be granted for kaolin in view of its excellent safety record despite continuous use as a food additive, pharmaceutical ingredient, personal hygiene component and in many industrial applications.

The applicant SOKA did not provide any long-term toxicity data based on the following justification: *"Aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not become bioavailable when ingested. Aluminium silicate has been, and still is used, extensively as an ingredient in anti-diarrhoeal medication. In Europe, Aluminium silicate is approved for use as an anti-caking agent in feed and has the feed additive number E559 for all animals feedingstuffs and all species or categories with no maximum concentration. Aluminium silicate is also listed in the internationally recognized Food Chemical Codex as a food additive. In view of the inert nature of Aluminium silicate, its natural occurrence, extremely low toxicity and chronic exposure in everyday life through medicines, toiletries and natural environment no long-term toxicity study is required. Information found in the public domain confirm the very low long-term/carcinogenicity of toxicity of Aluminium silicate."*

B.6.5.1 12 months study, inhalation route, Guinea pigs

Previous evaluation:	In DAR (2008)

Reference	: Schepers G.W.H., 1971	Exposure	:	12 months
Title of study	: Lung tumors of primates and rodents – Industrial Medicine, Vol. 40 (1), pp32-37.	Dose	:	Not reported
Test substance	: Kaolin, batch No. and purity not reported	Vehicle	:	Not reported
Administration way	: Tracheal injection	GLP statement	:	Not stated, published article
Species	: Guinea pigs; strain and origin not reported	Guideline	:	Not applicable
Group size	: 2 862 animals received 130 substances (or combinations of substances)	Acceptability	:	Supporting (limited reporting, major deviations from OECD 413 and 451)*
	Control group: 976 animals	NOAEL	:	Not reported
		NOEL	:	Not reported

***** The following deviations from the OECD TG 413 and 451 (2018) are noted:

- Exposure method was intratracheal injection.
- Limited reporting regarding exposure method and preparation of tested materials.
- Exposure was for 12 months - only one dose was tested.
- No information provided on animal number, sex and age per group.
- Body and organ weights were not reported.
- Haematology, clinical chemistry, urinalysis and histopathology and bronchoalveolar lavage fluid analysis were not performed.
- Limited reporting on histopathology methodology and results. No histological examination of nasopharyngeal tissues presented. Liver, kidneys, adrenals, brain, heart, aorta, kidneys, muscle, pituitary, thyroid, parathyroids, thymus, pancreas, testes, ovaries, accessory sex organs, tissues of the gastrointestinal tract, peripheral nerve, spinal cord, a section of bone-marrow and skin were not processed.

Material and methods

This paper presents several series of experimental animals exposed by tracheal injection and inhalation methods to a variety of chemical substances.

Kaolin ~~as a negative control~~ was administered by tracheal injection in guinea pigs.

2 862 animals received 130 different substances (or combinations of substances) by the intratracheal route. Kaolin was ~~used as~~ one of the tested ~~three control~~ materials.

The author evaluated the experimentally induced pulmonary lesions and classified them as neoplastic (N), epithelializations (E) or other lesions (O) according to their severity (+ slight reaction, ++ moderate reaction, +++ marked reaction).

Results

The results obtained with the guinea pigs are shown in Table B.6.5.1-1.

Table B.6.5.1-1: Lungs tumours experimentally induced in guinea pigs

Treated animals			Controls		
Number of animals	Tumours		Number of animals	Tumours	
	p.c.	%		p.c.	%
4294	11	0.26	1878	0	0

No ~~tumors~~ pulmonary lesions were observed in ~~the controls, including~~ the Kaolin treated group. Slight reactions to treatment ~~of~~ with Kaolin were observed in the lungs and were categorised as “other lesions”, but they were not detailed in the paper.

Conclusions

Intratracheal injection of a suspension or solution of any chemical substance is not necessarily pathogenic. It has often been argued that intratracheal injections create highly artificial local conditions that must necessarily induce pulmonary lesions. To a degree, the intratracheal method does exaggerate the biological effects of most substances. However, if the material is truly inert, this can be proven by the intratracheal method.

The tracheal method can be quite discriminative of biological effects produced by chemically or physically different materials.

Kaolin, administered during 12 months via intratracheal route to the guinea pig does not induce any epithelialization or neoplasia lesion.

Previous evaluation:	In DAR (2008)

B.6.5.2 24 months study, inhalation route, rats

Reference	: Wagner J.C., Griffiths D.M., Munday D.E.; 1987	Exposure	: ~~24~~ 12 months
Title of study	: Experimental studies with palygorskite dusts. Br. J. Ind. Med. 44:749-763.	Dose	: 10 mg/m^3, for 6 h/day for 5 day/week
Test substance	: Kaolin, batch No. and purity not reported. Crocidolite, Attapulgite	Vehicle	: Not reported
Administration way	: Inhalation	GLP statement	: Not stated, published article
Species	: Rat, Fischer F344, SPF	Guideline	: Not applicable
Group size	: 20 males and 20 females / groups	Acceptability	: Supporting (limited reporting, major deviations from OECD 413 and 451)*
		NOAEL	: Not reported
		NOEL	: Not reported

***** The following deviations from the OECD TG 413 and 451 (2018) are noted:

- Purity of tested chemicals not reported.
- Exposure was for 12 months, only one dose was tested and bronchoalveolar lavage fluid analysis was not performed.
- Limited information regarding housing, acclimatisation conditions and inhalation chamber volume.
- Body and organ weights were not reported.
- Haematology, clinical chemistry, urinalysis and histopathology were not performed.
- No histological examination of nasopharyngeal tissues.
- Adrenals, brain, heart, aorta, muscle, pituitary, thyroid, parathyroids, thymus, pancreas, testes, ovaries, uterus, accessory sex organs, tissues of the gastrointestinal tract, peripheral nerve, spinal cord, a section of bone-marrow and skin were not processed histopathologically.

Material and methods

Kaolin was used as a negative control in this inhalation study.

Test Material: the following dusts were used:

- Kaolin (coating grade): negative control coating grade kaolin obtained from English China Clays Company, prepared in their mills in St Austell, Cornwall.
- Crocidolite: positive control (standard reference sample of asbestos).
- Attapulgite: 2 different samples were tested, named by the region in which they were mined, Lebrija and Leicester. Both minerals belong to the palygorsite group of clays and are of fibrous character with a crystalline structure.

Materials were originally obtained either as rocks, granules or fine dusts. They were subsequently milled as required to size adequate for producing a dust cloud in the inhalation chamber. The respirable dusts were obtained *via* ultrasonic dispersion. Weighted samples of each dust were suspended in known volumes of distilled water and aliquots were passed through a filter with 25mm diameter and pore size of 0.2µm (Millipore) in a glass filter holder. To calculate the number of fibres/µg of dust, the filters were observed under a transmission electron microscope.

Since kaolin is not a fibrous dust, the authors provided the percentages of the different sizes of particles in the produced dust. They are presented in table B.6.5.1-1.

Table B.6.5.2-1: Percentages of particles' size ranges in the Kaolin dust

Size range (µm)	(%)
0.8-1.2	19.3
1.2-1.6	19.5
1.6-2.3	19.4
2.3-3.3	22.4
3.3-4.6	10.8
4.6-6.6	6.7
6.6-9.3	1.8
9.3-13.2	0.2

Wagner, Griffiths and Munday exposed 40 rats (20 males and 20 females) to Attapulgite dust in an inhalation chamber, at a concentration of 10 mg/m^3, for 6 h/day for 5 day/week ~~until they were killed~~. The exposure terminated after 12 months. At 3, 6, 12 and 24 months, four animals were killed and subjected to necropsy; the lungs, liver, spleen, kidneys and other relevant organs were examined microscopically. Mineralogical analysis, examination of ashed lung sections and examination of macerated lung tissue, were also performed. All remaining rats were allowed to live their life span.

Kaolin, the negative-control dust, and Crocidolite UICC, the positive-control dust, were also administered at a dose of 10 mg/m^3.

A group of 40 untreated rats (20 males and 20 females) was also included in the experiment as a control for the exposure procedure.

At the microscopic examination, the incidences of the following proliferative lesions and pulmonary neoplasms were recorded:

(1) bronchoalveolar hyperplasia - no malignant proliferation of the epithelia,

(2) benign alveolar neoplasm,

(3) malignant alveolar neoplasm,

(4) adenocarcinoma,

(5) squamous carcinoma,

(6) adenosquarnous carcinoma,

(7) mesothelioma.

Results

One peritoneal mesothelioma, one adenocarcinoma, and three bronchoalveolar hyperplasia were found in rats treated with Lebrija Attapulgite. Thirty-five rats had no proliferative changes. In rats treated with Leichester Attapulgite, proliferative lesions observed included two mesothelioma, one peritoneal mesothelioma, one malignant alveolar neoplasm, two benign alveolar neoplasms, and eight broncho-alveolar hyperplasias. Twenty-seven rats had no proliferative lesions. Rats in the positive-control Crocidolite group had one adenocarcinoma and three bronchoalveolar tumors. Two rats exposed to the negative-control Kaolin exhibited broncho-alveolar ~~tumors~~ hyperplasia but the authors state that this just indicative of an irritation reaction.

During the histological evaluation of formol-fixed pulmonary tissue, severity of fibrosis was recorded on an internationally accepted scale (Table B.6.5.1-3).

Table B.6.5.2-2: Degrees of pulmonary fibrosis

Grade	Effect
1	Normal
2	Dust in macrophages

3	Early interstitial reaction
4	First signs of fibrosis
5	Fibrosis +
6	Fibrosis ++
7	Fibrosis +++
8	Severe fibrosis

A reaction of 4 or more was considered to be indicative of fibrosis. The mean fibrosis grades of each treatment group are presented in Table B.6.5.2-3.

Table B.6.5.2-3: Toxicity of inhaled Attapulgite dust vs Kaolin

Dust source	Total No. of rats	Mean fibrosis grade as a function of time after exposure			
		3 months	6 months	12 months	24 months
Lebrija Attapulgite	40	3.1	2.6	3.2	3.2
Leicester Attapulgite	40	3.0	3.1	4.0	-
Kaolin	40	2.8	2.75	2.4	2.1
Crocidolite	40	4.1	3.3	3.1	3.8
Unexposed	40	1.25	1.75	1.0	1.2

(- Not done)

From the results in Table B.6.5.2-3, the authors conclude that only the Attapulgite from Leicester is potentially hazardous showing an increase in the mean fibrosis grade as a function of time after aexposure.

Conclusions

Kaolin, administered during 12 months to the rat in an inhalation chamber does not induce any malignant lesion.

Summary and conclusions on long-term toxicity and carcinogenicity

There are no GLP or guideline complying studies regarding long-term effects of Aluminium Silicate calcined. However, two published papers were submitted, a 12-month intratracheal study in Guinea pigs (Schepers, 1971), and a 24-month inhalation study in rats with Kaolin (Wagner *et al.*, 1987)~~, where the Kaolin was used as negative control~~. These studies ~~can be~~ were evaluated and regarded as supporting data by the RMS.

In the study by Schepers (1971), Kaolin, administered during 12 months *via* intratracheal route to the guinea pig ~~does~~ did not induce any epithelialization or neoplasia lesion. Intratracheal injections create highly artificial local conditions that must necessarily induce pulmonary lesions. To a degree, the intratracheal method does exaggerate the biological effects of most substances. However, if the material is truly inert, this can be proven by the intratracheal method.

In a 24-month inhalation study (Wagner *et al.*, 1987), Kaolin, administered during 12 months to the rat in an inhalation chamber did not induce any malignant lesion. There were only two incidences of broncho-alveolar hyperplasia in the total of 40 exposed rats which are considered to be reaction to an irritant according to the study author. This study on Kaolin is also included in the REACH dossier[4] for consideration in read-across to Kaolin, calcined and it is concluded that: "*None of 40 rats exposed to Kaolin dust at a concentration of 10 mg/m³ for 6 hours per day with exposure durations ranging from 3 months to 12 months showed tumour formation".*

[4] https://echa.europa.eu/registration-dossier/-/registered-dossier/13356/7/8

Table B.6.5-1: Summary of carcinogenicity studies with aluminium silicate

Species, Route, Duration	Test item	Dose	Endpoint	Reference
Guinea pig, Intratracheal route, 12 months	Kaolin (batch, purity not reported)	Not reported	No epithelialization or neoplastic lesions. No GLP. No Guideline. **Study acceptable as supporting information.**	Schepers, 1971 (DAR, 2008)
Rat, Inhalation, 12-months (+12 mths obs. period)	Kaolin (batch, purity not reported)	10 mg/m^3 (6 h/day, 5 day/week)	No malignant lesions. No GLP. No Guideline. **Study acceptable as supporting information.**	Wagner *et al.*, 1987 (DAR, 2008)

In the REACH dossier no data on Kaolin, calcined were available. However, a long-term feeding study for synthetic amorphous silica (SAS) by Takizawa *et al.* (1988) was considered for read-across and was briefly presented as follows:

"Three groups of rats and mice received Syloid 244 at dietary levels of 1.25, 2.5 and 5% for 103 and 93 weeks, respectively. This corresponded to average daily doses of 2000 mg/kg bw/day for the high-dose group of rats and to 4500 to 5800 mg/kg bw/day for the high-dose groups of female and male mice, respectively. The animals were in good condition throughout and showed high survival. The tumour responses in all organs of SAS-treated rats and mice were not statistically significantly different from the controls (Fisher´s exact test and Cochran-Armitage test for trend). Based on the negative results after long-term oral application of SAS, there is no evidence of a carcinogenic potential arising from ingestion of these amorphous minerals."

The full study report by Takizawa *et al.* (1988) was not available to the RMS for evaluation. Nevertheless, this study has been included in the RAR for Kieselgur (diatomaceous earth) (2019) concluding that SAS was not carcinogenic. The relevance of this study with SAS for the assessment of aluminium silicate is not clearly demonstrated.

Overall, the RMS considers that although there are no long-term GLP or guideline studies with Aluminium Silicate calcined, waiving of long-term toxicity/carcinogenicity studies is considered acceptable since aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not become bioavailable when ingested.

Limited evidence from literature data on Kaolin administration for 12 months in the guinea pig (tracheal injection) or the rat (inhalation chamber) indicated no increased incidences of malignant lesions. The NOAEC of 47.6 µg/L set for kaolin after a 14-day treatment *via* the inhalation route is used for AOEC setting for consideration in non-dietary risk assessment (see Section B.6.3).

B.6.6 REPRODUCTIVE TOXICITY (ANNEX IIA 5.6)

There are no available GLP and/or guideline complying reproductive toxicity studies, including effects on fertility and development, with Aluminium Silicate calcined.

The notifier SOKA provided no additional data based on the following justification:

"Aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not become bioavailable when ingested. Aluminium silicate has been, and still is used, extensively as an ingredient in anti-diarrhoeal medication. In Europe, Aluminium silicate is approved for use as an anti-caking agent in feed and has the feed additive number E559 for all

animals feedingstuffs and all species or categories with no maximum concentration. Aluminium silicate is also listed in the internationally recognized Food Chemical Codex as a food additive. In view of the inert nature of Aluminium silicate, its natural occurrence, extremely low toxicity and chronic exposure in everyday life through medicines, toiletries and natural environment no reproductive toxicity study is required. Information found in the public domain confirms the very low reproductive toxicity of Aluminium silicate."

The Notifier Tessenderlo Group N.V. refers to the study by Patterson & Staszak (1977) previously evaluated in the DAR noting also that *"Although no animal studies according to international regulatory guidelines have been performed, extensive contact with and use of aluminium silicate (kaolin) in day-to-day life, be it as a food additive, a pharmaceutical ingredient, an ingredient in cosmetics and toiletry or an industrial chemical, has never led to any reported cases of reproductive toxicity. Given the inert nature of this substance, its lack of oral absorption and therefore bioavailability, conducting new studies on reproductive toxicity may be considered scientifically unjustified."*

Previous evaluation:	In DAR (2008)

Reference	: Patterson E.C., Staszak D.J. 1977	**Exposure**	: 37 to 68 days, 69 to 85 days, and 96 to 117 days prior to fertilization and during gestation
Title of study	: Effects of geophagia (kaolin* ingestion) on the maternal blood and embryonic development in the pregnant rat	**Dose**	: 0, 20% Kaolin, iron supplemented 20% Kaolin added to the diet
Test substance	: Kaolin	**Vehicle**	: Laboratory Chow, Ralston Purina Company, St. Louis, Missouri
Administration way	: Oral *via* the diet	**GLP statement**	: no
Species	: Sprague-Dawley, ARS rats	**Guideline**	: Not according to guidelines
Group size	: 12 females/dose	**Acceptability**	: Yes, supporting information
		NOEL	: Not applicable No teratogenic effect was observed

* Chemical analysis of air-floated clay: SiO: 45.12%, Al_2O_3: 39.05%, TiO_2: 1.54%, Fe_2O_3: 0.47%, P_2O_5: 0.04%, CaO: 0.18%, K_2O: 0.07%, SO_3: 0.18%, Zn: 11 ppm, Loss of ignition: 13.48%.

Materials and methods

Groups of 12 Sprague-Dawley female rats were fed three diets: control diet, 20% Kaolin diet, or iron-supplemented 20% Kaolin diet. The diets were fed for 37 to 68 days, 69 to 85 days, and 96 to 117 days prior to fertilization and the same diets were fed for the duration of the gestation period.

Red blood cell count, microhematocrit and haemoglobin/100 mL of blood were determined for each rat.

The following data were recorded at birth for the pups born to females in each of the three groups: weight of each pup, length of each pup, number in each litter, morphological abnormalities if any.

Findings

The animals fed the 20% Kaolin diet had significant reductions in haemoglobin, hematocrit, and red blood cell levels, thus indicating maternal anaemia. Significant reduction in the birth weight of the pups was observed. The kaolin fed rats receiving an iron supplement maintained hematocrit, haemoglobin, red blood cell levels, and pup weight within the normal range.

The length of the pups was not significantly different among the three groups across time and no morphological abnormalities were observed in any of the pups.

Table B.6.6-1: Maternal body weight changes during the first 13 days of gestation of pregnant rats fed diets without clay, with clay and with clay and iron

	Experimental groups		
	Control (n=12)	**Kaolin (n=12)**	**Kaolin + Iron (n=11#)**
Average weight gain (g)	47.8 ± 3.9	44.8 ± 4.1	48.0 ± 3.5

One rat died.

Table B.6.6-2: Mean litter size, length and weight of pups born to rats fed three diets

	Experimental groups		
	Control (n=79)	**Kaolin (n=76)**	**Kaolin + Iron (n=87)**
Litter size	6.6 ± 3.8	6.3 ± 2.9	7.9 ± 2.5
Length (mm)	5.10 ± 0.12	5.03 ± 0.04	5.20 ± 0.34
Weight (g)	**6.4 ± 6.4**[#]	5.8*[$] ± 0.06	6.2 ± 0.52

* Significance level in comparison with the rats fed 20% kaolin + iron diet
[$] $P < 0.01$
the RMS considers that this might be a typographical error.

Conclusions

Considering the limited information included in this study, no effects on the development of foetuses are anticipated from exposure of pregnant rats to clay. Moreover, litter size was comparable among control and treated groups suggesting that no substantial effects on fertility are also expected from oral ingestion of clay.

~~No teratogenic effects of kaolin were observed in this study.~~

Summary and conclusions on reproductive toxicity

There are no GLP or guideline complying studies regarding reproductive toxicity of Aluminium Silicate calcined.

Limited information on reproductive toxicity of clay is provided in literature study by Patterson & Staszak, 1977. In this study, no effects on the development of foetuses (foetal weight, foetal length) are anticipated from exposure of pregnant rats to clay. Moreover, litter size was comparable among control and treated groups suggesting that no substantial effects on fertility are also expected from oral ingestion of clay.

Table B.6.6-1: Summary of the reproductive toxicity study with aluminium silicate

Species, Route, Duration	**Test item**	**Dose**	**Endpoint**	**Reference**
Rat, Oral (geophagia), Duration: 37 to 68 days, 69 to 85 days, and 96 to 117 days prior to fertilization and	Kaolin (batch, purity not reported)	0, 20% Kaolin, iron supplemented 20% Kaolin added to the diet	No effects on foetal development. No effects on litter size suggesting that no substantial effects on fertility are also expected from oral ingestion of clay. No GLP. No Guideline.	Patterson & Staszak, 1977 (DAR, 2008)

Species, Route, Duration	Test item	Dose	Endpoint	Reference
during gestation			**Study acceptable as supporting information.**	

B.6.7 NEUROTOXICITY

No study was submitted, not required.

The applicant SOKA provided no additional data based on the following justification:

"Aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not become bioavailable when ingested. Aluminium silicate has been, and still is used, extensively as an ingredient in anti-diarrhoeal medication. In Europe, Aluminium silicate is approved for use as an anti-caking agent in feed and has the feed additive number E559 for all animals feedingstuffs and all species or categories with no maximum concentration. Aluminium silicate is also listed in the internationally recognized Food Chemical Codex as a food additive. In view of the inert nature of Aluminium silicate, its natural occurrence, extremely low toxicity and chronic exposure in everyday life through medicines, toiletries and natural environment no neurotoxicity study is required."

The applicant Tessenderlo Group N.V. provided no additional data based on the following justification:

"No specific neurotoxicity studies on aluminium silicate (kaolin) were available.

Kaolin is internationally approved for medical, cosmetic and industrial use across the world, which is generally considered as safe. Kaolin is also listed for food use in the internationally recognised "Food Chemicals Codex". There is no evidence for absorption or bioavailability and therefore neurotoxicity studies should not be required.

As a general note, to address the potential for toxicity for the first inclusion of aluminium silicate (kaolin) under Directive 91/414, many of the provided cases referred to aluminium silicate being a commonly used food additive within the EU. Through Regulation (EU) No. 380/2012 (enforced from 1st February 2014) amending Annex II to Regulation (EC) No. 1333/2008, the use of a number of aluminium-containing food additives was restricted. Among these were calcium aluminium silicate, bentonite and aluminium silicate (kaolin), which are no longer permitted to be used as food additives within the EU. A transitionary period until 1st August 2014 was established by the regulation to allow manufacturers time to comply with the requirements, given the extensive use of aluminium compounds as coatings and colourants in existing produced food items.

As such, it is no longer considered appropriate to rely on such cases at renewal (which were based on kaolin being an approved food additive within the EU). Following the removal of aluminium silicate from the EU list of approved food additives, EFSA commented on the impact of the ruling on several aluminium-compound containing plant protection products (including aluminium silicate). The comments made at the '15th BfR Consumer Protection Forum' indicate that where negligible exposure is demonstrated, the continued use of aluminium silicate as an insecticide on grape vines could be supported within the EU. Furthermore, the EFSA presentation noted that "Aluminium silicate could be considered a candidate for the inclusion in Annex IV of Commission Regulation (EC) No 396/2005"."

The RMS considers that waiving of neurotoxicity studies is considered acceptable since aluminium silicate is a natural inorganic mineral. It is inert, insoluble in aqueous and organic solvents. It does not

become bioavailable when ingested. Moreover, it does not belong to the chemical class of organophosphorus compounds nor does it have a neurotoxic mode of pesticidal action.

B.6.8 OTHER TOXICOLOGICAL STUDIES

No further toxicological studies were submitted.

B.6.8.1 Toxicity studies on metabolites

No other toxicological studies on aluminium silicate calcined are available. It is not absorbed after ingestion or topical application, it is therefore not bioavailable and there are no metabolites.

B.6.8.2 Supplementary studies on the active substance

Previous evaluation:	None; submitted by SOKA for the purpose of the a.s. renewal

The EFSA CONTAM Panel has noted (EFSA Journal 2009; 7(11):1391) that "*Kaolin is not allergenic, although it is known to induce pro-inflammatory responses which have been particularly noticed for the lung following intratracheal administration (Yanagisawa et al., 2007)*". In this context, on the request of the RMS, this study was provided by the notifier and it is summarized below:

Authors	Yanagisawa R., Takano H., Ichinose T., Mizushima K., Nishikawa M., Mori I., Inoue K., Sadakane K. and Yoshikawa T.
Year	2007
Tittle	Gene expression analysis of murine lungs following pulmonary exposure to Asian sand dust particles
Source	Exp Biol Med (Maywood) 2007 Sep;232(8):1109-18
Guidelines	Not reported
Deviations	Not reported
GLP	Not reported

Materials and methods:

The aim of this study was to examine the effects of Asian sand dust particles (ASDPs) on gene expression in the murine lung using microarray analysis and elucidated the components responsible for lung inflammation. Male ICR mice were intratracheally administrated ASDPs, heat-treated ASDPs (ASDP-F, lipopolysaccaride (LPS), or b-glucan free), or kaolin particles. A microarray analysis for murine lungs was performed, the results of which were confirmed by quantitative reverse transcription–polymerase chain reaction (RT-PCR). The protein expression and histologic changes were also assessed.

Details on the test articles' composition are included in the following table:

Table Σφάλμα! Χρησιμοποιήστε την καρτέλα "Κεντρική σελίδα", για να εφαρμόσετε το Titre 2 στο κείμενο που θέλετε να εμφανίζεται εδώ.**-2: Contents of elements in particles**

	Element fraction (%)	
Components	ASDPs	Koalin
SiO_2	60.0	45.4
Al_2O3	11.1	38.8
Fe_2O_3	4.1	0.3
Na_2O_3	1.8	0.1
CaO	9.0	0.1
MgO	2.5	None
TiO_2	0.7	1.5
K_2O	2.2	Trace
Loss on ignition	8.6	13.8

Results and Conclusions:

Kaolin administration upregulated the expression of several proinflammatory genes (CXCL1/ KC and CXCL2/MIP-2) and proteins (CXCL1/KC, CXCL2/MIP-2, CCL3/MIP-1a, and CXCL10/IP-10). Both ASDP and kaolin induced neutrophil infiltration into the alveolar space, mediated by CXC chemokines. Gene and protein expression of proinflammatory molecules eventually lead to neutrophilic lung inflammation.

Neutrophilic lung inflammation was less severe in the case of kaolin, presumably due to the structure of kaolin being multilayered and highly porous.

B.6.8.3 Endocrine disrupting properties

In order to determine whether aluminium silicate calcined exhibits ED properties, the RMS has considered the assessment strategy proposed in the EFSA/ECHA Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No. 528/2012 and (EC) No. 1107/2009 (EFSA Journal 2018;16(6):5331).

Aluminium silicate as a natural inorganic mineral, it is inert, insoluble in aqueous and organic solvents and it does not become bioavailable when ingested. Consequently, it is not distributed in the tissues and it is not metabolized. On the basis of this argumentation, short-term, long-term/carcinogenicity and reproductive toxicity data were not provided and were not considered necessary.

Thus, although EATS-mediated adversity has not been sufficiently investigated, no particular concern is raised, and no further data are required. There is no information from the US-EPA Chemistry Dashboard[5] on endocrine activity.

Thus, due to the knowledge on ADME and physico-chemical properties of aluminium silicate, an ED assessment for humans does not appear scientifically necessary and testing for this purpose is not considered technically possible (reference to Figure 1, Note b of the ECHA/EFSA Guidance for the identification of endocrine disruptors in the context of Regulations (EU) No 528/2012 and (EC) No 1107/2009).

B.6.9 MEDICAL DATA

B.6.9.1 Medical surveillance on manufacturing plant personnel and monitoring studies

A large-scale epidemiologic survey is available on the effects of kaolin in the United States (Rawlings, 1997). The survey included more than 95 % of the kaolin workers in the US employed in the mining and processing of kaolin. No case of primary sensitivity was found as a result of exposure to kaolin in its solid, liquid or respirable forms. Some cases of pneumoconiosis were reported in the late 1970's

[5] https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID30107899

and 1980's, which were the result of exposure far in excess of current ACGIH TLVs (American Conference of Governmental Industrial Hygienists; Threshold Limit Values), dating in some cases back to the 1930's. With good dust control practices over the last 25 years no new cases of kaolin caused pneumoconiosis were found. ~~Supportive evidence can be drawn from studies of English china clay workers by Oldham and Comyns[6].~~

Supportive evidence can be drawn from studies of English china clay workers by Oldham *et al.*, 1989[2]. In this study, employees and pensioners from the largest china clay industry in south west England were subjected to chest x-ray examinations, underwent ventilatory capacity tests and completed occupational histories and respiratory symptoms questionnaires. The x-ray readings were analysed to seek relations between the incidences of pulmonary health effects and occupational exposure.

The authors categorised employment into groups with similar dust exposure levels and measured dust concentrations at various production locations. The amount of respirable dust varies from a low level where the clay is being processed as a slurry to a higher level when the clay is being dried or milled. All results from sampling for more than 2 years, along with estimated respirable dust concentration of the general population (normal living) are summarised in Table B.6.9.1-1

Table B.6.9.1-1: Average respirable dust concentration measurements and numbers of samples taken for the different types of production locations in the China clay industry of South west England from January 1984 to March 1986.

Location type	No of samples	Average dust (mg/m^3)
Dryers	681	1.9
Attritor mills	114	2.7
Calciners	63	2.5
Slurry plants*	69	1.1
Tube presses	5	0.5
Normal living	-	Typically less than 0.3

*this is an assumed average figure based on regular sampling at the older and dustier of the two slurry plants and a small number of samples from the modern, less dusty plant.

In addition, the x-rays from 3689 workers and pensioners were read 'blindly' by three independent readers and scored according to the standard ILO classification of radiographs of pneumoconiosis [7]. The categories of x-ray reads were then converted to numerical scores based on a scale from 0 to 3, where 0 refers to the absence of small opacity and 3 represents the most profuse. Only 8.5% of them exhibited an x-ray score of category 1 or more and out of them, 43% had potentially dusty jobs. In addition, 10 of the 39 category 2 reads and 3 in a total of 5 category 3 reads were from pensioners, indicating that there must be a progressive effect of dust exposure in the lung. The natural logarithm of the numerical x-ray score as the dependent variable was then regressed against duration of employment in the grouped job categories and in non-dusty life. The results from the analysis are depicted in Table B.6.9.1-2.

Table B.6.9.1-2: Regression coefficients of 1000 x $\log_e$ (Radiological score) on years of exposure

Job classification	No of subjects: 3689	Regression coefficient	Std error
Non-dusty life	1064	6	0.4

[6] Ogle, CJ, Rundle, EM and Sugar ET (1989). China clay workers in the south west of England: analysis of chest radiograph readings, ventilatory capacity, and respiratory symptoms in relation to type and duration of occupation. British Journal of Industrial Medicine 1989; 46:261-270

[7] International Labour Office. Guidelines for the use of *International Classification of Radiographs of Pneumoconiosis*. Geneva: ILO, 1980. Occupational Safety and Health Series No. 22 (Rev).

Job classification	No of subjects: 3689	Regression coefficient	Std error
Dryers:			
Pre-1971	522	25	2
Post-1971	997	14	1
Slurry	325	8	1
Calciners:			
Pre-1971	83	-1	4
Post-1971	202	10	3
Pan kilns	248	13	2
China stone mills	37	51	6
Attritor mills:			
Pre-1971	138	44	4
Post-1971	73	23	4

The authors point out that since the 1970's many operational changes have been introduced in order to improve airborne dust control and to reduce the generated amount of dust during production processes, therefore they decided to make a distinction between 'early' and 'late' dust exposure by using 01/01/1971 as the dividing date. During this period the older drying processes (pan kilns) were phased out while grinding and flotation of china stone also came to an end.

Employment in mills has the greatest effect on x-ray categorisation, followed by the dryers. This is consistent with the average respirable dust concentrations (Table B.6.9.1-1). Employment in calciners, however, had a low effect despite the relatively high dust concentration, which may be related to the fact that calcinated kaolin no longer has the crystalline structure and form of hydrous kaolin (calcined kaolin can be considered amorphous). In china stone mills, the occupation with the highest regression coefficient, despite the low number of subjects, the incidences of pneumoconiosis were high (14 out of 37 employers had a radiological score of >1). The RMS considers that based on the available evidence, the increased incidence of pneumoconiosis among individuals exposed to china stone, is most likely attributed to the presence of quartz in the inhaled dust which, in the case of china stone may reach up to 25% while its composition in china clay is less than 1%.

In summary, the authors conclude that the average worker in any of the occupations in china clay industry under current conditions (after 1971) is not expected to develop category 1 pneumoconiosis throughout a full working life.

Previous evaluation:	None; submitted by SOKA for the purpose of the a.s. renewal

The notifier SOKA provided the following statement regarding employees working over the past nine years on the production site of Aluminium silicate and its representative formulation SOKALCIARBO WP:

"N*o adverse health effects resulting from exposure to Aluminium silicate and its representative formulation SOKALCIARBO WP was reported*".

B.6.9.2 Data collected on humans

No clinical cases and poisoning incidents are available.

Previous evaluation:	None; submitted by SOKA for the purpose of the a.s. renewal

According to a statement provided by the notifier SOKA:

"No adverse health effects resulting from exposure to Aluminium silicate and its representative formulation SOKALCIARBO WP was reported. There is no evidence or data available to support any findings in relation to poisoning with Aluminium silicate."

B.6.9.3 Direct observations

A large scale epidemiologic survey is available on the effects of Aluminium silicate in the United States (Rawlings, 1997). The survey included more than 95 % of the Aluminium silicate workers in the US employed in the mining and processing of Aluminium silicate. No case of primary sensitivity was found as a result of exposure to Aluminium silicate in its solid, liquid or respirable forms. Some cases of pneumoconiosis were reported in the late 1970's and 1980's, which were the result of exposure far in excess of current ACGIH TLVs, dating in some cases back to the 1930's. With good dust control practices over the last years no new cases of Aluminium silicate caused pneumoconiosis were found.

The RMS notes that details on the epidemiological survey are not included in the dossier of either notifier. Instead, a letter by Rawlings (1997) is provided by Tessenderlo Group N.V. as evidence of the information stated above (previously included in the DAR).

B.6.9.4 Epidemiological studies

The applicant SOKA provided no additional information.

The applicant Tessenderlo Group N.V. stated that: *"The general population is routinely exposed to kaolin in medicines, cosmetics and industrial applications. No major health effects have been reported from kaolin in the general population. Exposure of the general population to significant levels of kaolin dust, that may be potentially harmful through inhalation or eye irritation, is highly unlikely."*

B.6.9.5 Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests

The applicant SOKA stated that: *"Specific signs of poisoning or clinical tests are not known nor not expected."*

The applicant Tessenderlo Group N.V. stated that: *"Not applicable; aluminium silicate (kaolin) is not acutely toxic. No cases of poisoning incidents with aluminium silicate (kaolin) have been reported."*

B.6.9.6 Proposed treatment: first aid measures, antidotes, medical treatment

The applicant SOKA provided the following information:

"Due to the nature and low toxicity of Aluminium silicate, no special antidotes or medical treatment.

First aid measures:

- *Eye contact: Rinse with copious quantities of water and seek medical attention if irritation persists.*
- *Inhalation: Go to fresh air. If symptoms appear, seek medical attention.*
- *Ingestion: No special first aid measures necessary.*
- *Skin contact: No special first aid measures necessary.*

- *Most important symptoms and effects, both acute and delayed: No acute and delayed symptoms and effects are observed.*
- *Indication of any immediate medical attention and special treatment needed: No specific actions are required."*

The applicant Tessenderlo Group N.V. provided the following information:

- *"Inhalation exposure:*

Remove to fresh air. If breathing becomes laboured administer oxygen. If breathing stops administer artificial respiration. Obtain immediate medical attention.

- *Skin contact:*

Remove contaminated clothing. Flush skin with large amounts of water. Obtain medical attention if irritation develops.

- *Eye contact:*

Irrigate immediately with water for 10 - 15 minutes. Obtain medical attention if irritation persists.

- *Ingestion:*

Obtain medical attention immediately. Only induce vomiting at the instruction of a physician. Never give anything by mouth to an unconscious person."

B.6.9.7 Expected effects of poisoning

The applicant SOKA stated that: "*Due to the nature and low toxicity of Aluminium silicate, no expected effects of poisoning".*

The applicant Tessenderlo Group N.V. provided the following information:

- *"Inhalation exposure:*

No cases known; may cause irritation to the mucous membranes of the respiratory tract. Prolonged (i.e. > 10 years) and repeated exposure such as those experienced by kaolin mineworkers may cause lung damage if no, or improper, protection from dust is taken.

- *Skin contact:*

Transient irritation of the skin may occur. This may be exacerbated if the affected area is not washed.

- *Eye contact:*

Transient irritation may result from brief exposure to the powder or dilute (spray) formulation. This may be exacerbated if the affected area is not washed.

- *Ingestion:*

No cases of poisoning are known. Kaolin is used in over-the-counter anti-diarrhoeal preparations. Transient effects on the digestive system may occur."

B.6.10 REFERENCES RELIED ON

Active substance -SOKA

Reference List by Data Point

Data point	Author(s)	Year	Title Source (where different from company) Compagny, Report No GLP or GEP (where relevant), Published	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection	Owner	Previous submission/ evaluation
K-CA 5.2.1/01	[redacted]	2016a	Kaolin: acute oral toxicity in the rat – fixed dose method [redacted] GLP: Yes Published: No	Y	Y	New study for renewal dossier - confirmatory data	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal
K-CA 5.2.2/01	[redacted]	2016b	Kaolin: acute dermal toxicity (limit test) in the rat [redacted] GLP: Yes Published: No	Y	Y	New study for renewal dossier - confirmatory data	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal
K-CA 5.2.3/01	[redacted]	2016	Kaolin: acute inhalation toxicity (nose only) study in the rat [redacted] GLP: Yes Published: No	Y	Y	New study for renewal dossier - confirmatory data	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal

Data point	Author(s)	Year	Title Source (where different from company) Compagny, Report No GLP or GEP (where relevant), Published	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection	Owner	Previous submission/ evaluation
K-CA 5.2.6/01	[redacted]	2016c	Kaolin: local lymph node assay in the mouse – pooled method [redacted] GLP: Yes Published: No	Y	Y	Study required according to Regulation (EU) no. 283/2013	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal
K-CA 5.3.3/01	[redacted]	2019	Study Plan: Kaolin and Kaolinitic Clay: Toxicity Study by Inhalation administration to Han Wistar Rats for 2 Weeks [redacted] GLP: Yes Published: No	Y	Y	Study required according to Regulation (EU) no. 283/2013	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal
K-CA 5.4.1/01	Wisher, M.	2017	Kaolin: Reverse Mutation Assay 'Ames Test' using *Salmonella typhimurium* and *Escherichia coli* ENVIGO, Report No. LF13TQ GLP: Yes Published: No	N	Y	Study required according to Regulation (EU) no. 283/2013	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal

Data point	Author(s)	Year	Title Source (where different from company) Compagny, Report No GLP or GEP (where relevant), Published	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection	Owner	Previous submission/ evaluation
K-CA 5.8.2/01	Yanagisawa R., Takano H., Ichinose T., Mizushima K., Nishikawa M., Mori I., Inoue K., Sadakane K. and Yoshikawa T.	2007	Gene expression analysis of murine lungs following pulmonary exposure to Asian sand dust particles Exp Biol Med (Maywood) 2007 Sep;232(8):1109-18 GLP: No Published: Yes	N	N	-	Public literature	

Reference List by Author

Author(s)	Data point	Year	Title Source (where different from company) Company, Report No GLP or GEP (where relevant), Published	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection	Owner	Previous submission/ evaluation
[redacted]	K-CA 5.2.1/01	2016a	Kaolin: acute oral toxicity in the rat – fixed dose method [redacted] GLP: Yes Published: No	Y	Y	New study for renewal dossier - confirmatory data	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal

Author(s)	Data point	Year	Title Source (where different from company) Company, Report No GLP or GEP (where relevant), Published	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection	Owner	Previous submission/ evaluation
[redacted].	K-CA 5.2.2/01	2016b	Kaolin: acute dermal toxicity (limit test) in the rat [redacted] GLP: Yes Published: No	Y	Y	New study for renewal dossier - confirmatory data	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal
[redacted]	K-CA 5.2.6/01	2016c	Kaolin: local lymph node assay in the mouse – pooled method [redacted] GLP: Yes Published: No	Y	Y	Study required according to Regulation (EU) no. 283/2013	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal
[redacted]	K-CA 5.2.3/01	2016	Kaolin: acute inhalation toxicity (nose only) study in the rat [redacted] GLP: Yes Published: No	Y	Y	New study for renewal dossier - confirmatory data	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal
[redacted]	K-CA 5.3.3/01	2019	Study Plan: Kaolin and Kaolinitic Clay: Toxicity Study by Inhalation administration to Han Wistar Rats for 2 Weeks [redacted] GLP: Yes Published: No	Y	Y	Study required according to Regulation (EU) no. 283/2013	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal

Author(s)	Data point	Year	Title Source (where different from company) Company, Report No GLP or GEP (where relevant), Published	Vertebrate study Y/N	Data Protection Claimed Y/N	Justification if data protection	Owner	Previous submission/ evaluation
Wisher, M.	K-CA 5.4.1/01	2017	Kaolin: Reverse Mutation Assay 'Ames Test' using *Salmonella typhimurium* and *Escherichia coli* ENVIGO, Report No. LF13TQ GLP: Yes Published: No	N	Y	Study required according to Regulation (EU) no. 283/2013	KPC-Europe aisbl	Submitted for the purpose of the a.s. renewal
Yanagisawa R., Takano H., Ichinose T., Mizushima K., Nishikawa M., Mori I., Inoue K., Sadakane K. and Yoshikawa T.	K-CA 5.8.2/01	2007	Gene expression analysis of murine lungs following pulmonary exposure to Asian sand dust particles Exp Biol Med (Maywood) 2007 Sep;232(8):1109-18 GLP: No Published: Yes	N	N	-	Public literature	

In addition, reference was made to data already evaluated at EU Peer Review of Aluminium Silicate:

- Hungary, 2008. Draft Assessment Report on the active substance Aluminium silicate prepared by the rapporteur Member State Hungary in the framework of Council Directive 91/414/EEC, August 2008
- Hungary, 2011: Final addendum to the Draft Assessment Report on the active substance Aluminium silicate prepared by the rapporteur Member State Hungary in the framework of Council Directive 91/414/EEC, May 2011
- EFSA, 2012: Conclusion on the peer review of the pesticide risk assessment of the active substance aluminium silicate, EFSA Journal 2012;10(2):2517

Active substance – TESSENDERLO

Reference List by Data Point

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	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
KCA 5.2.1/01	[redacted].	1997a	Satintone® 5HB, Lot #10146 "Calcined Kaolin" - Acute Oral Toxicity Limit Test. [redacted] Report number4903 GLP Unpublished.	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
KCA 5.2.1/02	[redacted]	1997b	M-96-018, Lot #08145 - Acute Oral Toxicity Limit Test. [redacted] Report number 5003. GLP Unpublished	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
KCA 5.2.2/01	[redacted].	1997c	Satintone® 5HB, Lot #10146 - Acute Dermal Toxicity Limit Test. [redacted] Report number 4904. GLP	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)

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	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
			Unpublished					
KCA 5.2.3/01	[redacted]	1997d	M-97-009, Lot #09255 "Calcined Kaolin"- Acute Inhalation Toxicity Limit Test. [redacted] Report number: 5405. GLP Unpublished	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
KCA 5.2.3/02	[redacted]	1997e	M-96-018 - Acute Inhalation Toxicity Limit Test. [redacted] Report number 5424. GLP Unpublished	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
KCA 5.2.4/01	[redacted]	1997f	M-96-018, Lot #08145 - Primary Skin Irritation. [redacted] Report number 4906. GLP Unpublished	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
KCA 5.2.5/01	[redacted]	1997g	M-96-018, Lot #08145 - Primary Eye Irritation. [redacted]	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)

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	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
			[redacted] Report number 4905 GLP Unpublished					
KCA 5.2.5/02	[redacted]	2000	Surround® WP Crop Protectant - Primary Eye Irritation Study in Rabbits. [redacted]. Report number 9914 GLP Unpublished	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
KCA 5.2.6/01	[redacted]	2017	Assessment of sensitising properties on albino guinea pigs. Maximisation test according to Magnusson and Kligman. Report number SMK-PH-17/0024 R1 GLP Unpublished	Y	Y	New data not previously submitted	Tessenderlo Kerley Inc.	Submitted for the purpose of the a.s. renewal
KCA 5.5/01	Schepers, G.W.H.	1971	Lung tumors of primates and rodents Industrial Medicine, Vol. 40 (1), pp32-37. No report number Not GLP Published	N	N	-	Public	In DAR (2008)
KCA 5.5/02	Wagner, J.C., Griffiths, D.M.,	1987	Experimental studies with palygorskite dusts.	N	N	-	Public	In DAR (2008)

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	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
	Munday, D.E.		Br. J. Ind. Med. 44:749-763 No report number Not GLP Published					
KCA 5.6/01	Patterson, E.C., Staszak, D.J.	1977	Effects of geophagia (kaolin ingestion) on the maternal blood and embryonic development in the pregnant rat. J. Nut. 107:2020-2025 No report number Not GLP Published	N	N	-	Public	In DAR (2008)
KCA 5.7	Committee on Food Chemicals Codex	1996	Food Chemicals Codex – Fourth Edition 208/FCC IV/Monograph Specifications No report number Not GLP Published	N	N	-	Public	In DAR (2008)
KCA 5.9.1/01	Rawlings, W. Jr.	1997	Letter to J L Etheridge Washington County Internal Medicine P.C. No report number Not GLP Unpublished	N	N	N	Tessenderlo Group N.V.	In DAR (2008)
KCA 5.9.1/02	Ogle, C.J., Rundle, E.M. and Sugar, E.T.	1989	China clay workers in the south west of England: analysis of chest radiograph readings, ventilatory	N	N	-	Public	Submitted for the purpose of the a.s. renewal

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	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
			capacity, and respiratory symptoms in relation to type and duration of occupation. British Journal of Industrial Medicine 1989; 46:261-270 No report number Not GLP Published					

Reference List by Author

Author(s)	Data point	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
Committee on Food Chemicals Codex	KCA 5.7	1996	Food Chemicals Codex – Fourth Edition 208/FCC IV/Monograph Specifications No report number Not GLP Published	N	N	-	Public	In DAR (2008)
[redacted]	KCA 5.2.5/02	2000	Surround® WP Crop Protectant - Primary Eye Irritation Study in Rabbits. [redacted]	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)

Author(s)	Data point	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
			Report number 9914 GLP Unpublished					
Ogle, C.J., Rundle, E.M. and Sugar, E.T.	KCA 5.9.1/02	1989	China clay workers in the south west of England: analysis of chest radiograph readings, ventilatory capacity, and respiratory symptoms in relation to type and duration of occupation. British Journal of Industrial Medicine 1989; 46:261-270 No report number Not GLP Published	N	N	-	Public	Submitted for the purpose of the a.s. renewal
Patterson, E.C., Staszak, D.J.	KCA 5.6/01	1977	Effects of geophagia (kaolin ingestion) on the maternal blood and embryonic development in the pregnant rat. J. Nut. 107:2020-2025 No report number Not GLP Published	N	N	-	Public	In DAR (2008)
Rawlings, W. Jr.	KCA 5.9.1/01	1997	Letter to J L Etheridge Washington County Internal Medicine P.C. No report number Not GLP Unpublished	N	N	N	Tessenderlo Group N.V.	In DAR (2008)
[redacted]	KCA 5.2.6/01	2017	Assessment of sensitising properties on albino guinea pigs. Maximisation test	Y	Y	New data not previously	Tessenderlo Kerley Inc.	Submitted for the purpose of

Author(s)	Data point	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
			according to Magnusson and Kligman. Report number SMK-PH-17/0024 R1 GLP Unpublished			submitted		the a.s. renewal
Schepers, G.W.H.	KCA 5.5/01	1971	Lung tumors of primates and rodents Industrial Medicine, Vol. 40 (1), pp32-37. No report number Not GLP Published	N	N	-	Public	In DAR (2008)
Wagner, J.C., Griffiths, D.M., Munday, D.E.	KCA 5.5/02	1987	Experimental studies with palygorskite dusts. Br. J. Ind. Med. 44:749-763 No report number Not GLP Published	N	N	-	Public	In DAR (2008)
[redacted].	KCA 5.2.1/01	1997a	Satintone® 5HB, Lot #10146 "Calcined Kaolin" - Acute Oral Toxicity Limit Test. [redacted] Report number4903 GLP Unpublished.	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
[redacted]	KCA 5.2.1/02	1997b	M-96-018, Lot #08145 - Acute Oral Toxicity Limit Test. [redacted]	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)

Author(s)	Data point	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
			[redacted] Report number 5003. GLP Unpublished					
[redacted]	KCA 5.2.2/01	1997c	Satintone® 5HB, Lot #10146 - Acute Dermal Toxicity Limit Test. [redacted] Report number 4904. GLP Unpublished	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
[redacted].	KCA 5.2.3/01	1997d	M-97-009, Lot #09255 “Calcined Kaolin”- Acute Inhalation Toxicity Limit Test. [redacted] Report number: 5405. GLP Unpublished	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
[redacted]	KCA 5.2.3/02	1997e	M-96-018 - Acute Inhalation Toxicity Limit Test. [redacted] Report number 5424.	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)

Author(s)	Data point	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Data protection claimed Y/N	Justification if data protection is claimed	Owner	Previous submission/ evaluation
			GLP Unpublished					
[redacted]	KCA 5.2.4/01	1997f	M-96-018, Lot #08145 - Primary Skin Irritation. [redacted] GLP Unpublished	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)
[redacted].	KCA 5.2.5/01	1997g	M-96-018, Lot #08145 - Primary Eye Irritation. [redacted] Report number 4905 GLP Unpublished	Y	N	N	Tessenderlo Group N.V.	In DAR (2008)

APPENDIX I: STANDARD TERMS AND ABBREVIATIONS

Part 1 Technical Terms

A	ampere
ACH	acetylcholine
AChE	acetylcholinesterase
ADI	acceptable daily intake
ADP	adenosin diphosphate
AE	acid equivalent
AFID	alkali flame-ionization detector or detection
A/G	albumin/globulin ratio
ai	active ingredient
ALD_{50}	approximate median lethal dose, 50 %
ALT	alanine amitrotransferase (SGPT)
AMD	automatic multiple development
ANOVA	analysis of variance
AOEL	acceptable operator exposure level
AP	alkaline phosphatase
approx	approximate
ARC	anticipated residue contribution
ARfD	acute reference dose
as	active substance
AST	aspartate aminotransferase (SGOT)
ASV	air saturation value
ATP	adenosine triphosphate
BCF	bioconcentration factor
bfa	body fluid assay
BOD	biological oxygen demand
bp	boiling point
BSAF	biota-sediment accumulation factor
BSE	bovine spongiform encephalopathie
BSP	bromosulfophthalein
Bt	bacillus thuringiensis
Bti	bacillus thuringiensis israelensis
Btk	bacillus thuringiensis kurstaki
Btt	bacillus thuringiensis tenebrionis
BUN	blood urea nitrogen
bw	body weight
c	centi- (x 10^{-2})
°C	degree celsius (centigrade)
CA	controlled atmosphere
CAD	computer aided design
CADDY	computer aided dossier and data supply (an electronic dossier interchange and archiving format)
cd	candela
CDA	controlled drop(let) application
cDNA	complementary DNA
CEC	cation exchange capacity
cf	confer, compare to
CFU	colony forming units
ChE	cholinesterase
CI	confidence interval
CL	confidence limits

cm	centimetre
CNS	central nervous system
COD	chemical oxygen demand
CPK	creatinine phosphatase
cv	coeficient of variation
Cv	ceiling value
CXL	Codex Maximum Residue Limit (Codex MRL)
d	day
DES	diethylstilboestrol
DFR	dislodgeable foliar residue
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
dna	designated national authority
DO	dissolved oxygen
DOC	dissolved organic carbon
dpi	days pot inoculation
DRES	dietary risk evaluation system
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
dw	dry weight
DWQG	drinking water quality guidelines
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
ECD	electron capture detector
ECU	European currency unit
ED_{50}	median effective dose
EDI	estimated daily intake
ELISA	enzyme linked immunosorbent assay
e-mail	electronic mail
EMDI	estimated maximum daily intake
EPMA	electron probe micro analysis
ERC	environmentally relevant concentration
ERL	extraneous residue limit
F	field
F_0	parental generation
F_1	filial generation, first
F_2	filial generation, second
FIA	fluorescence immuno assay
FID	flame ionization detector
FOB	functional observation battery
fp	freezing point
FPD	flame photometric detector
FPLC	fast protein liquid chromatography
g	gram
G	glasshouse
GAP	good agricultural practice
GC	gas chromatography
GC-EC	gas chromatography with electron capture detector
GC-FID	gas chromatography with flame ionization detector
GC-MS	gas chromatography-mass spectrometry
GC-MSD	gas chromatography with mass-selective detection
GEP	good experimental practice
GFP	good field practice
GGT	gamma glutamyl transferase

GI	gastro-intestinal
GIT	gastro-intestinal tract
GL	guideline level
GLC	gas liquid chromatography
GLP	good laboratory practice
GM	geometric mean
GMO	genetically modified organism
GMM	genetically modified micro-organism
GPC	gel-permeation chromatography
GPPP	good plant protection practice
GPS	global positioning system
GSH	glutathion
GV	granulosevirus
h	hour(s)
H	Henry`s Law constant (calculated as a unitless value) (see also K)
ha	hectare
Hb	haemoglobin
HCG	human chorionic gonadotropin
Hct	haematocrit
HDT	highest dose tested
hL	hectolitre
HEED	high energy electron diffraction
HID	helium ionization detector
HPAEC	high performance anion exchange chromatography
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HPLC-MS	high pressure liquid chromatography – mass spectrometry
HPPLC	high pressure planar liquid chromatography
HPTLC	high performance thin layer chromatography
HRGC	high resolution gaschromatography
Hs	Shannon-Weaver index
Ht	haematocrit
I	indoor
I_{50}	inhibitory dose, 50 %
IC_{50}	median immobilization concentration
ICM	integrated crop management
ID	ionization detector
IEDI	international estimated daily intake
IGR	insect growth regulator
im	intramuscular
inh	inhalation
ip	intraperitoneal
IPM	integrated pest management
IR	infrared
ISBN	international standard book number
ISSN	international standard serial number
iv	intravenous
IVF	in vitro fertilization
k	kilo
K	Kelvin or Henry`s Law constant (in athmospheres per cubic meter per mole) (see also H)13
K_{ads}	adsorption constant
K_{des}	apparent desorption coefficient
K_{oc}	organic carbon adsortion coefficient

K_{om}	organis matter adsorption coefficient
kg	kilogram
L	litre
LAN	local area network
LASER	light amplification by stimulated emission
LBC	loosely bound capacity
LC	liquid chromatography
LC-MS	liquid chromatography-mass spectrometry
LC_{50}	lethal concentration, median
LCA	life cycle analysis
LCLo	lethal concentration low
LC-MS-MS	liquid chromatography with tandem mass spectrometry
LD_{50}	lethal dose, median; dosis letalis media
LDLo	lethal dose low
LDH	lactate dehydrogenase
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of determination
LOEC	lowest observable effect concentration
LOEL	lowest observable effect level
LOQ	limit of quantification (determination)
LPLC	low pressure liquid chromatography
LSC	liquid scintillation counting or counter
LSD	least squared denominator multiple range test
LSS	liquid scintillation spectrometry
LT	lethal threshold
m	metre
M	molar
µm	micrometer (micron)
MC	moisture content
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentratin
MCV	mean corpuscular volume
MDL	method detection limit
MFO	mixed function oxidase
µg	microgram
mg	milligram
MHC	moisture holding capacity
min	minute(s)
mL	millilitre
MLT	median lethal time
MLD	minimum lethal dose
mm	millimetre
mo	month(s)
mol	Mol
MOS	margin of safety
mp	melting point
MRE	maximum residue expected
MRL	maximum residue limit or level
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MSDS	material safety data sheet
MTD	maximum tolerated dose
n	normal (defining isomeric configuration)

NAEL	no adverse effect level
nd	not detected
NEDI	no effect daily intake (mg/kg body wt/day)
NEL	no effect level
NERL	no effect residue level
ng	nanogram
nm	nanometer
NMR	nuclear magnetic resonance
no	number
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOED	no observed effect dose
NOEL	no observed effect level
NOIS	notice of intend to suspend
NPD	nitrogen-phosphorus detector or detection
NPV	nuclear polyhedrosis virus
NR	not reported
NTE	neurotoxic target esterase
OC	organic carbon content
OCR	optical character recognition
ODP	ozone-depleting potential
ODS	ozone-depleting substances
OM	organic matter content
op	organophosphorus pesticide
Pa	pascal
PAD	pulsed amperometric detection
2-PAM	2-pralidoxime
pc	paper chromatography
PC	personal computer
PCV	haematocrit (packed corpuscular volume)
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PED	plasma-emissions-detektor
pH	pH-value
PHED	pesticide handler`s exposure data
PHI	pre-harvest interval
PIC	prior informed consent
pic	phage inhibition capacity
PIXE	proton inducted X-ray emission
pK_a	negative logarithm (to the base 10) of the dissociation constant)
PNEC	predicted no effect concentration
po	by mouth (per os)
P_{ow}	partition coefficient between n-octanol and water
POP	persistent organic pollutants
ppb	parts per billion (10^{-9})
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
ppq	parts per quadrillion (10-24)
ppt	parts per trillion (10^{-12})

PSP	phenolsulfophthalein
PrT	prothrombin time
PRL	practical residue limit
PT	prothrombin time
PTDI	provisional tolerable daily intake
PTT	partial thromboplastin time
QSAR	quantitative structure-activity relationship
r	correlation coefficient
r^2	coefficient of determination
RBC	red blood cell
REI	restricted entry interval
R_f	ratio of fronts
RfD	reference dose
RH	relative humidity
RL_{50}	residual lifetime
RNA	ribonucleic acid
RP	reversed phase
rpm	reversed phase material
rRNA	ribosomal ribonucleic acic
RRT	relative retention time
RSD	relative standard deviation
s	second
SAC	strong adsorption capacity
SAP	serum alkaline phosphatase
SAR	structure/activity relationship
SBLC	shallow bed liquid chromatography
sc	subcutaneous
sce	sister chromatid exchange
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SEP	standard evaluation procedure
SF	safety factor
SFC	supercritical fluid chromatography
SFE	supercritical fluid extraction
SIMS	secondary ion mass spectroscopy
SOP	standard operating procedures
sp	species (only after a generic name)
SPE	solid phase extraction
SPF	specific pathogene free
spp	subspecies
sq	square
SSD	sulfur specific detector
SSMS	spark source mass spectrometry
STEL	short term exposure limit
STMR	supervised trials median residue
t	tonne (metric ton)
$t_{1/2}$	half-life (define method of estimination)
T_3	tri-iodothyroxine
T_4	thyroxine
TADI	temporary acceptable daily tntake
TBC	tightly bound capacity
TCD	thermal conductivity detector
TCLo	toxic concentration low

TID	thermionic detector, alkali flame detector
TDLo	toxic dose low
TDR	time domain reflectrometry
TER	toxicity exposure ration
TER_I	toxicity exposure ration for initial exposure
TER_{ST}	toxicity exposure ration following repeated exposure
TER_{LT}	toxicity exposure ration following chronic exposure
tert	tertiary (in a chemical name)
TEP	typical end-use product
TGGE	temperature gradient gel electrophoresis
TIFF	tag image file format
TLC	thin layer chromatography
Tlm	median tolerance limit
TLV	threshold limit value
TMDI	theoretical maximum daily intake
TMRC	theoretical maximum residue contribution
TMRL	temporary maximum residue limit
TOC	total organic chlorine
Tremcard	Transport emergency card
tRNA	transfer riboncleic acid
TSH	thyroid stimulating hormone (thyrotropin)
TWA	time weighted average
UDS	unscheduled DNA synthesis
UF	uncertainly factor (safety factor)
ULV	ultra low volume
UV	ultraviolet
v/v	volume ratio (volume per volume)
WBC	white blood cell
wk	week
wt	weight
w/v	weight per volume
w/w	weight per weight
XRFA	X-ray fluorescence analysis
yr	year
<	less than
≤	less than or equal to
>	greater than
≥	greater than or equal to

Part 2 Organisations and Publications

ACPA	American Crop Protection Association
ACTM	American Society for Testing and Materials
BA	Biological Abstracts (Philadelphia)
BART	Beneficial Arthropod Registration Testing Group
CA	Chemical Abstracts
CAB	Centre for Agriculture and Biosciences International
CAC	Codex Alimentarius Commission
CAS	Chemical Abstracts Service
CCFAC	Codex Committee on Food Additives and Contaminants
CCGP	Codex Committee on General Principles
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Food
CE	Council of Europe

CIPAC	Collaborative International Pesticides Analytical Council Ltd
COREPER	Comite des Representants Permanents
EC	European Commission
ECB	European Chemical Bureau
ECCA	European Crop Care Association
ECDIN	Environmental Chemicals Data and Information of the European Communities
ECDIS	European Environmental Chemicals Data and Information System
ECE	Economic Commission for Europe
ECETOC	European Chemical Industry Ecology and Toxicology Centre
ECLO	Emergency Centre for Locust Operations
ECMWF	European Centre for Medium Range Weather Forecasting
ECPA	European Crop Protection Association
EDEXIM	European Database on Export an Import of Dangerous Chemicals
EHC (number)	Environment Health Criteria (number)
EHCD	Environmental Health Criteria Document
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EMIC	Environmental Mutagens Information Centre
EPA	Environmental Protection Agency
EPO	European Patent Office
EPPO	European and Mediterranean Plant Protection Organization
ESCORT	European Standard Characteristics of Beneficials Regulatory Testing
EU	European Union
EUPHIDS	European Pesticide Hazard Information and Decision Support System
EUROPOEM	European Predictive Operator Exposure Model
FAO	Food and Agriculture Organization of the UN
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
FRAC	Fungicide Resistance Action Committee
GATT	General Agreement on Tariffs and Trade
GAW	Global Atmosphere Watch
GCOS	Global Climate Observing System
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GEDD	Global Environmental Data Directory
GEMS	Global Environmental Monotoring System
GIEWS	Global Information and Early Warning System for Food and Agriculture
GIFAP	Groupement International des Association Nationales de Fabricants de Produits Agrochimiques (now known as GCPF)
GRIN	Germplasm Resources Information Network
HRAC	Herbicide Resistance Action Committee
IARC	International Agency for Research on Cancer
IATS	International Academy of Toxicological Science
IBT	Industrial Bio-Test Laboratories
ICBB	International Commissin of Bee Botany
ICBP	International Council for Bird Preservation
ICES	International Council for the Exploration of the Seas
ICPBR	International Commissin for Plant-Bee Relationships
ILO	International Labour Organization
IMO	International Maritime Organisation
IOBC	International Organization for Biological Control of noxious Animals and Plants
IPCS	International Programme on Chemical Safety
IRAC	Insecticide Restistance Action Committee
IRC	International Rice Commission

ISCO	International Soil Conservation Orginazation
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
JECFA	FAO/WHO Joint Expert Committee on Food Additives
JFCMP	Joint FAO/WHO Food and Animal Feed Contamination Monitoring Programme
JMP	Joint Meeting on Pesticdes (WHO/FAO)
JMPR	Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Expert Group on Pesticide Residues (Joint Meeting on Pesticide Residues)
NATO	North Atlantic Treaty Organisation
NAFTA	North American Free Trade Agreement
NCI	National Cancer Institute (USA)
NCTR	National Center for Toxicological Research (USA)
NGO	non-governmental organization
NTP	National Toxicology Programme (USA)
OECD	Organization for Economic Cooperation and Development
OLIS	On-line Information Service of OECD
PAN	Pesticides Action Network
RNN	Re-registration Notification Network
RTECS	Registry of Toxic Effects of Chemical Substances (USA)
SCPH	Standing Committee on Plant Health
SETAC	Society of Environmental Toxicology and Chemistry
SI	Systeme International d`Unites
SITC	Standard International Trade Classification
TOXLINE	Toxicology Information On-line
UN	United Nations
UNEP	United Nations Environment Programme
WCDP	World Climate Data Programmme
WCP	Workd Climate Programme
WCRP	World Climate Research Programme
WFP	World Food Programme
WHO	World Health Organization
WTO	World Trade Organization
WWF	World Wide Fund for Nature

APPENDIX II: SPECIFIC TERMS AND ABBREVIATIONS

ADME	adsorption, distribution, metabolism and excretion
ADR	European agreement concerning the international carriage of dangerous goods by road
AR	applied radioactivity
AUC	area under curve
CHO	Chinese hamster ovary
EC	emulsifiable concentrate
EVOH	ethyl vinyl alcohol
DPDB	Data Protection Database (PSD)
HDPE	high density polyethylene
HPT	hypothalamus-pituitary-testicular
K_{ads}	adsorption constant
K_F	freudlich coefficient
K_{OH}	hydroxyl radical rate constant
K_{OW}	octanol water partition coefficient
LH	Luteinizing Hormone
LOQ	limit of quantification
MATC	Maximum Acceptable Toxic Concentration
MMAD	mass median aerodynamic diameter
Mbq	Mega becquerels
MS	Member State
MWHC	maximum water holding capacity
NMS	Northern Member State
OM	Organic Matter
P_0 / P_1	parental generation, first (author dependent)
PDE	potential dermal exposure
PEC_a	predicted environmental exposure in air
PEC_{gw}	predicted environmental exposure in ground water
PEC_s	predicted environmental exposure in soil
PEC_{sw}	predicted environmental exposure in surface water
PHED	Pesticide Handlers Exposure Database
pKa	dissociation constant
POEM	Predictive Operator Exposure Model
PPE	personal protective equipment
r^2	correlation coefficient
RSD	relative standard deviation
s	second
TER	toxicity exposure ratio
TLC	thin layer chromatography

APPENDIX III: LITERATURE DATA BY TESSENDERLO GROUP N.V.

(summary report as submitted by the applicant)

LITERATURE DATA

Introduction

Under Article 8(5) of Regulation 1107/2009, a literature review must be submitted as part of the renewal dossier for plant protection products:

"Scientific peer-reviewed open literature, as determined by the Authority, on the active substance and its relevant metabolites dealing with side-effects on health, the environment and non-target species and published within the last ten years before the date of dossier submission shall be added by the applicant to the dossier".

In compliance with Article 8.5 of Regulation (EC) No 1107/2009 and Part A of Commission Regulation (EU) No 283/2013, a search of the scientific peer reviewed open literature relative to aluminium silicate (kaolin) was performed and included in the dossier.

The literature search was performed between 1 November 2017 and 15 November 2017.

The search was organised in two parts, with an initial search focusing on identifying literature relative to aluminium silicate, kaolin and derivatives, including trade names, and a final part focusing on identifying literature relevant to each compartment of the dossier. Details of the search term, data mining strategies and results are presented herewith.

Literature search timing

Literature search span: the search was limited to the period spanning from 1 January 2005 (year of submission of the original Aluminium silicate (kaolin) inclusion dossier) until 8 November 2017. The search therefore covered eleven years and ten months of peer-reviewed publications and was performed less than six months before renewal dossier submission deadline (28 February 2018).

Methodology

- **Search environment**

The literature search was performed on the following databases: CAB, PubMed, Toxnet and Science Direct. In addition, relevant documents from Google, Google Scholar, ECHA, ResearchGate and the United States Environmental Protection agency database were downloaded and processed separately.

- **Identification of peer-reviewed literature pertaining to the Chemical Active aluminium silicate (kaolin)**

The reference collections were queried by name, with a typical query string presented below.

Typical name query	Kaolin OR "china clay" OR kaolinite OR "calcined kaolin" OR "hydrous kaolin" OR "Aluminium silicate" OR "Aluminum silicate" OR Aluminosilicate OR "Satintone 5HB" OR "Surround WP" OR "Sokalciarbo WP" OR "Argical Pro" OR "Agri Jardin".

Underlined text refers to trade names of aluminium silicate-containing products.

In addition, the following CAS numbers were included in the search:

Identification number (List)	Identity
1318-74-7 (CAS)	Kaolinite
1332-58-7 (CAS)	Kaolin
296-473-8 (EC)	Kaolin, calcined
310-194-1 (EC)	Kaolin
92704-41-1 (CAS)	Kaolin, calcined

The topics of interest, such as human toxicity, fate, residues, etc., were not included as a key element of the search strategy. Often an event or outcome is not explicitly described by the subject at the title or abstract level and it would be difficult to adequately describe the individual toxic effects one can envisage using key words and/or subject headings in a complex search query. Therefore, a sequential approach was preferred, and once a pool of documents referencing the chemical active had been identified and duplicates removed, a different approach was used to identify relevant literature.

Identification of relevant literature in the selected peer-reviewed literature

The search strategy highlighted 14,796 documents of potential interest to this literature review upon execution, including 676 from non-peer-reviewed literature. These were dismissed. The remaining 14120 documents contained a number of duplicates as a result of searching the reference collections separately.

To identify which of these 14,796 records mentioned the aspects of interest to this particular project, a pipeline of processing resources (PR) was applied to each document in turn and only those which specifically mentioned toxic effects, environmental fate and behaviour, etc., of kaolin or its common variants, were identified as a positive result. This granular information was captured during the text processing phase using customised gazetteer lists such as the extract given in Appendix I[8].

Each PR focused on a specific compartment. Search terms used in each PR are presented in Appendix I.

Each PR performs a different function and in general terms the approach taken was to Tokenise (identify individual words and features) and Sentence-split the documents; use the Gazetteer lists to identify any important key words and phrases such as dietary exposure; identify the Title and Abstract part of the document; look within the Title and Abstract for patterns matching the natural language expressions describing to the toxic effects of each active substance on humans, for example; and index the results. The rules used to identify these passages of text also make a simple allowance for co-referencing where we try to associate a word or phrase (the anaphor) with a previously mentioned entity (the antecedent). This technique was used to assist with the questions on Residue and Human Toxicity at the Sentence level only. The results of the search were loaded into Microsoft Excel and duplicate records removed using several algorithms.

The entire collection of records was clustered to help with the identification of common themes and the output (network visualisation and density heat map) is provided in Figures 1 and 2.

[8] Please note that the imbedded text files can only be opened in the .docx version of this document.

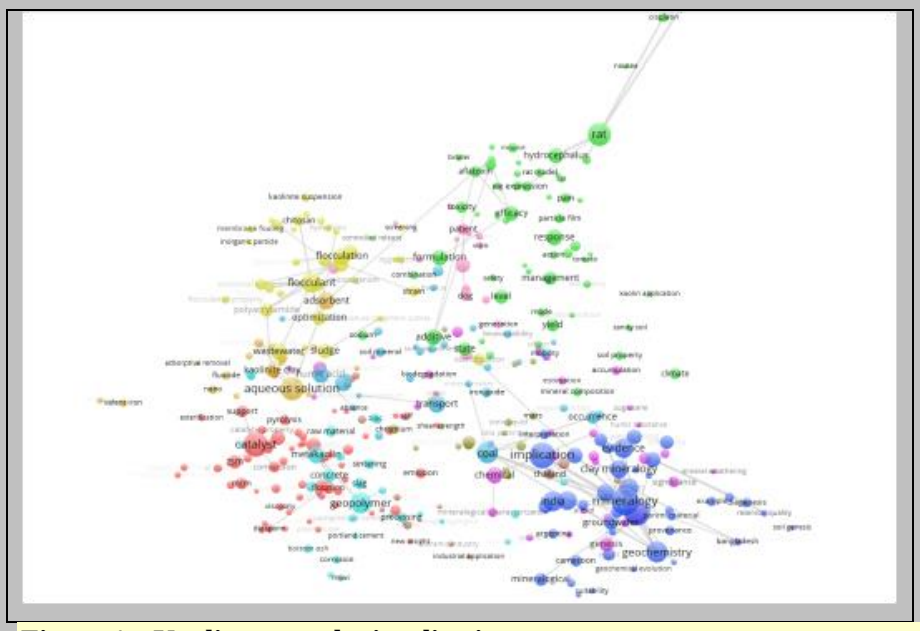


Figure 1: Kaolin network visualisation

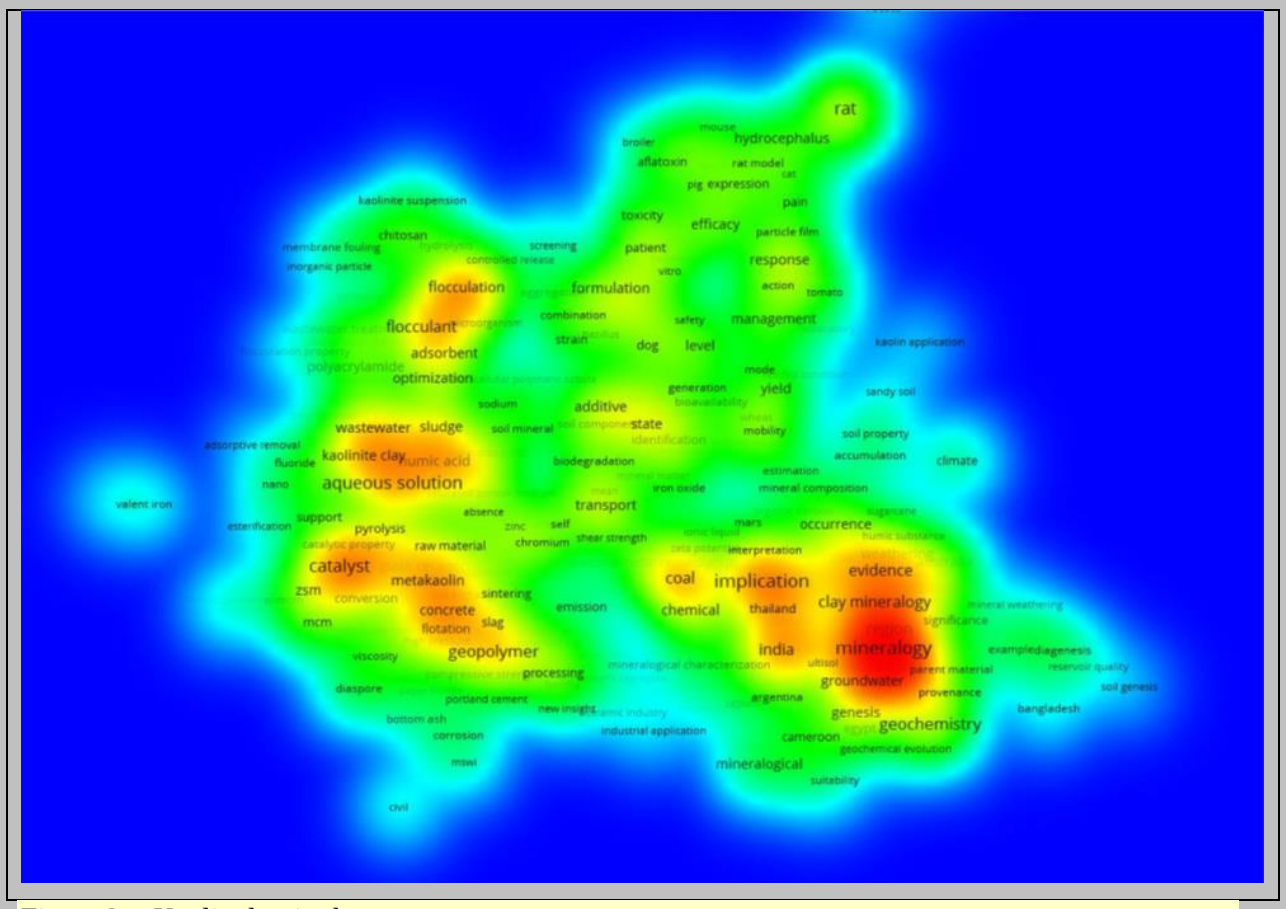


Figure 2: Kaolin density heat map

- **Results**

As a result of applying the text mining pipeline to the document corpus, a number of documents were identified as being of potential relevance to the four questions fundamental to the project, toxicity,

ecotoxicology, fate & behaviour, and residues. No potentially relevant documents were identified for the Occupational health and safety category.

The following tables summarise the total number of documents retrieved from each reference collection noting that the total count in Table 2 will include duplicate records found in two or more reference collections. The results presented in Table 3 refer to unique records and show the number of documents identified by text mining as potentially relevant.

Table 1: Number of documents retrieved from each reference location*

Reference Collection	**Total Document Retrieved**
CAB	4,396
PubMed	2,873
ScienceDirect	6,807
Toxnet	44
Total	14,120

*: includes duplicate documents

Table 2: Number of documents identified as potentially relevant by text mining

Compartment	**Unique Documents Identified**
Toxicity	301
Residues	52
Environmental Fate	248
Ecotoxicity	241

For each compartment described in Table 2, an excel spreadsheet was provided. Each potentially relevant entry consisted of one line, split into several columns: Database source and record number, date of publication, title, journal reference and author, URL and abstract.

The lists were screened for potential relevance, i.e. references that did not appear to be relevant based on title or abstract only were dismissed.

The remaining references were obtained and screened for relevance again.

- **Lists of relevant and non-relevant articles by dossier sections (only Mammalian Toxicology is included in this section)**

Mammalian Toxicology evaluation table (relevant articles)

Section	Authors	Year	Title	Source (Journal, volume, pages)	Fulfils data requirement?	Comments	Discussion on relevance
M-CA Section 5	Adamis Z., Williams R. B.	2005	Bentonite kaolin and selected clay minerals.	Environmental Health Criteria SN - 9241572310 SN - 0250-863X. PY - 2005 IS - No.231 SP - xvi + 175 pp. PB - World Health Organization LA - English CY - Geneva	No	Review set out to: (i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits; (ii) to identity new or potential pollutants; (iii) to identify gaps in knowledge concerning the health effects of pollutants; (iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.	This 2005 review is not used in the dossier since all studies quoted in this review are old (none post-2003, most pre-1990) and would probably not be considered acceptable by Klimisch score. It is freely available at https://www.who.int/ipcs/publications/ehc/ehc_231.pdf. The review itself is sufficient as supporting evidence since it confirms that kaolin is not acutely toxic, not toxic to reproduction, not genotoxic and not carcinogenic when not contaminated with crystalline silica and that no report of local or systemic adverse effects has been identified from the extensive use of kaolin in cosmetics.

Mammalian Toxicology evaluation table (non-relevant articles)

Authors	Year	Title	Source (Journal, volume, pages)	Fulfils data requirement?	Comments	Discussion on relevance
Hummel TZ1, Kindermann A, Stokkers PC, Benninga MA, ten Kate FJ.	2014	Exogenous pigment in Peyer patches of children suspected of having IBD; Exogenous pigment in Peyer patches of children suspected of having IBD.	J Pediatr Gastroenterol Nutr. 2014 Apr;58(4):477-80	No	An investigation of the distribution of exogenous pigment throughout the gastrointestinal tract of children suspected of having inflammatory bowel disease.	Not relevant, inflammatory bowel disease in children study, a speculative association with micro-particles was concluded.
Jung BG, Lee JA, Lee BJ.	2013	Antiviral effect of dietary germanium biotite supplementation in pigs experimentally infected with porcine reproductive and respiratory syndrome virus.	J Vet Sci. 2013;14(2):135-41	No	The effects of Germanium biotite (GB) on immune responses in a mouse model, were assessed to demonstrate the clearance effects of GB against Porcine reproductive and respiratory syndrome virus (PRRSV) in experimentally infected pigs as	Not relevant, Germanium biotite (GB) used.

Authors	Year	Title	Source (Journal, volume, pages)	Fulfils data requirement?	Comments	Discussion on relevance
					an initial step towards the development of a feed supplement that would promote immune activity and help prevent diseases.	
Abbès S, Ouanes Z, ben Salah-Abbès J, Houas Z, Oueslati R, Bacha H, Othman O.	2006	The protective effect of hydrated sodium calcium aluminosilicate against haematological biochemical and pathological changes induced by Zearalenone in mice.	Toxicon. 2006 Apr;47(5):567-74.	No	The findings suggested that deleterious effects of Zearalenone could be overcome or, at least, significantly were diminished by HSCAS.	Not relevant, hydrated sodium calcium aluminosilicate used.
Ali L, Idrees M1, Ali M, Hussain A, Ur Rehman I, Ali A, Iqbal SA, Kamel EH.	2014	Inhibitory effect of kaolin minerals compound against hepatitis C virus in Huh-7 cell lines.	BMC Res Notes. 2014 Apr 17;7:247.	No	Kaolin mineral derivatives showed promising inhibitory effects against HCV genotypes 3a and 1a infection, which suggested a possible use as complementary and alternative medicine for HCV viral infection.	Not relevant, kaolin derived anti-HCV compounds were used to decrease the hepatitis C virus titre in vitro.
Attik G, Brown R, Jackson P, Creutzenberg O, Aboukhamis I, Rihn BH.	2008	Internalization cytotoxicity apoptosis and tumor necrosis factor-alpha expression in rat alveolar macrophages exposed to various dusts occurring in the ceramics industry.	Inhal Toxicol. 2008 Sep;20(12):1101-12	No	Various ceramic dusts were tested in a rat alveolar macrophage (AM) cell. Cell death was assessed.	Not relevant, ceramic dusts used.
Awad ME, López-Galindo A, Setti M, El-Rahmany MM, Iborra CV.	2017	Kaolinite in pharmaceutics and biomedicine.	Int J Pharm. 2017 Nov 25;533(1):34-48	No	A review of some medical uses of kaolinite. It can be considered as a promising natural geomaterial for designing new derivatives that can contribute in the trials of discovering new therapeutic systems and treatment pathways.	Not relevant, as it describes the already varied uses of kaolinite in pharmaceutical applications.
Bart C. De Jonghe; Maureen P.Lawler; Charles C. Horn; Michael G.Tordoff	2009	Pica as an adaptive response: Kaolin consumption helps rats recover from chemotherapy-induced illness	Physiology & Behavior, Volume 97, Issue 1, 20 April 2009, Pages 87-90	No	Cisplatin induced chemical injury in rats could be beneficial to recovery,	Not relevant, paper describes a rat model treated with cisplatin with some recovery aided by clay consumption.
Bock-GieJung; Nguyen TatToan; Sun-JuCho; Jae-hyungKo; Yeon-KwonJung; Bong-JooLee	2010	Dietary aluminosilicate supplement enhances immune activity in mice and reinforces clearance of porcine circovirus type 2 in experimentally infected pigs	Veterinary Microbiology, Volume 143, Issues 2–4, 14 July 2010, Pages 117-125	No	The study aimed to evaluate immune enhancing effects of dietary aluminosilicate supplement (DAS) in mice, and to demonstrate clearance effects of DAS against porcine circovirus type 2 (PCV2) in experimentally infected pigs	Not relevant, DAS used: SiO2 (61.90%), Al2O3 (23.19%), Fe2O3 (3.97%) and Na2O (3.36%).

Authors	Year	Title	Source (Journal, volume, pages)	Fulfils data requirement?	Comments	Discussion on relevance
Bowman PD, Wang X, Meledeo MA, Dubick MA, Kheirabadi BS.	2011	Toxicity of aluminum silicates used in hemostatic dressings toward human umbilical veins endothelial cells HeLa cells and RAW267.4 mouse macrophages. ; Toxicity of aluminum silicates used in hemostatic dressings toward human umbilical veins endothelial cells HeLa cells and RAW267.4 mouse macrophages.	J Trauma. 2011 Sep;71(3):727-32	No	Human umbilical vein endothelial cells HeLa cells, and RAW267.4 mouse macrophage-like cells were incubated directly with different concentrations of each mineral (hydrous aluminum silicate particles) for 24 hours.	Not relevant, the study looked at in vitro cell death as an endpoint, kaolin was the less toxic than the other substances tested. However, the model does not appear to take into account normal mammalian physiological parameters.
Diaz D. E., Smith T. K.	2005	Mycotoxin sequestering agents: practical tools for the neutralisation of mycotoxins.	The mycotoxin blue book SN - 1904761194. PY - 2005 SP - 323-339 PB - Nottingham University Press LA - English CY - Nottingham	No	A review on mycotoxin decontamination from feedstuffs.	Not relevant, work on zeolites and other sequestering agents.
Edwards JV, Prevost N.	2011	Thrombin production and human neutrophil elastase sequestration by modified cellulosic dressings and their electrokinetic analysis. ; Thrombin production and human neutrophil elastase sequestration by modified cellulosic dressings and their electrokinetic analysis.	J Funct Biomater. 2011 Dec 15;2(4):391-413	No	Examination of the effects on wound healing of various surgical dressings.	Not relevant, kaolin-treated materials including a commercial haemorrhage control dressing (Quick Clot Combat Gauze) were used but no specific details was given on the kaolin used.
Gershkovich P, Darlington J, Sivak O, Constantinides PP, Wasan KM.	2009	Inhibition of intestinal absorption of cholesterol by surface-modified nanostructured aluminosilicate compounds. ; Inhibition of intestinal absorption of cholesterol by surface-modified nanostructured aluminosilicate compounds.	J Pharm Sci. 2009 Jul;98(7):2390-400	No	An examination of the ability of aqueous suspensions of surface-modified nanostructured aluminosilicate (NSAS) compounds to reduce the intestinal absorption of cholesterol in a rat model.	Not relevant, Protonated nanostructured aluminosilicate (NSAS)used.
Habold C, Reichardt F, Le Maho Y, Angel F, Liewig N, Lignot JH,	2009	Clay ingestion enhances intestinal triacylglycerol hydrolysis and non-esterified fatty acid absorption.	Br J Nutr. 2009 Jul;102(2):249-57	No	Previous work had shown Rats fed an elemental diet with 10% kaolinite had greater body-mass gain after 14 d. Based on this study the explanation might then be that increased NEFA absorption in kaolinite-fed rats leads to an	Not relevant because the basic findings are already well known and the work on NEFA is too speculative.

Authors	Year	Title	Source (Journal, volume, pages)	Fulfils data requirement?	Comments	Discussion on relevance
Oudart H.					increase in lipid accretion.	
Kato T, Toyooka T, Ibuki Y, Masuda S, Watanabe M, Totsuka Y.	2017	Effect of physicochemical character differences on the genotoxic potency of kaolin.	Genes Environ. 2017 May 1;39:12	No	Intratracheal administration of high doses of three types of kaolin to mice.	Not relevant, intratracheal administration of high doses of three types of kaolin. This is an unrealistic model with which to test genotoxicity.
Londono SC, Hartnett HE, Williams LB.	2017	Antibacterial Activity of Aluminum in Clay from the Colombian Amazon. ; Antibacterial Activity of Aluminum in Clay from the Colombian Amazon.	Environ Sci Technol. 2017 Feb 21;51(4):2401-2408.	No	Al toxicity plays a central role in the antibacterial action of a kaolin-rich clay from the Colombian Amazon (AMZ).	Not relevant, not kaolin, poorly defined clay -AMZ Clay used.
Pavel Gershkovich; Olena Sivak; Susana Contreras-Whitney; Jerald W.Darlington; Kishor M. Wasan	2012	Assessment of Cholesterol Absorption Inhibitors Nanostructured Aluminosilicate and Cholestyramine Using In Vitro Lipolysis Model	Journal of Pharmaceutical Sciences, Volume 101, Issue 1, January 2012, Pages 291-300	No	The effect of protonated nanostructured aluminosilicate (NSAS) on modeled intraluminal distribution of cholesterol was assessed using an in vitro lipolysis model.	Not relevant, fused aluminosilicate particles used.
Priest ND, Hoel DG, Brooks PN.	2006	Relative toxicity of chronic irradiation by 45Ca beta particles and 242Cm alpha particles with respect to the production of lung tumors in CBA/Ca mice.	Radiat Res. 2006 Nov;166(5):782-93.	No	Mice were exposed by inhalation to radiolabelled fused aluminosilicate particles and the responses of the lungs assessed.	Not relevant, poorly defined material used.
Reichardt F, Chaumande B, Habold C, Robin JP, Ehret-Sabatier L, Le Maho Y, Liewig N, Angel F, Lignot JH.	2012	Kaolinite ingestion facilitates restoration of body energy reserves during refeeding after prolonged fasting. ; Kaolinite ingestion facilitates restoration of body energy reserves during refeeding after prolonged fasting.	Fundam Clin Pharmacol. 2012 Oct;26(5):577-88.	No	Clay ingestion appears to be beneficial for individuals undergoing extreme nutritional conditions such as refeeding and limited food supplies.	Not relevant. Effects of kaolinite ingestion are well known. However, the description of the effects on re-feeding are of interest for medical uses.
Reichardt F, Habold C, Chaumande B, Ackermann A, Ehret-Sabatier L,	2009	Interactions between ingested kaolinite and the intestinal mucosa in rat: proteomic and cellular evidences.	Fundam Clin Pharmacol. 2009 Feb;23(1):69-79	No	The study showed that kaolinite particles ingested as a food complement interacted with the intestinal mucosa to modify nutrient absorption.	Not relevant. Effects of kaolinite ingestion are in the public domain and commonly understood.

Authors	Year	Title	Source (Journal, volume, pages)	Fulfils data requirement?	Comments	Discussion on relevance
Le Maho Y, Angel F, Liewig N, Lignot JH.						
Ridha Ben Ali; Anouar Ounis; Dorra Ben Said; Chadli Dziri; Michèle Véronique; El May	2017	Gastroprotective effects of Tunisian green clay on ethanol-induced gastric mucosal lesion in rats	Applied Clay Science, Volume 149, 1 December 2017, Pages 111-117	No	A study of the biological effects of green clay was administered orally followed by administration of ethanol 95% to induce a gastric ulcer. A potential gastroprotective activity on ethanol induced gastric mucosal lesions was found.	Not relevant, Natural Green Clay used (specification not known), not kaolin.
Samir Abbès; Zouhour Ouanes; Jalila Ben Salah-Abbès; Mosaad A. Abdel-Wahhab; RidhaOueslati; Hassen Bacha	2007	Preventive role of aluminosilicate clay against induction of micronuclei and chromosome aberrations in bone-marrow cells of Balb/c mice treated with Zearalenone	Mutation Research/Genetic Toxicology and Environmental Mutagenesis, Volume 631, Issue 2, 28 July 2007, Pages 85-92	No	The study investigated ability of hydrated sodium calcium aluminosilicate (HSCAS) to protect Balb/c mice against cytotoxicity and genotoxicity induced by Zearalenone.	Not relevant, hydrated sodium calcium aluminosilicate (HSCAS) used.
Sivak O, Darlington J, Gershkovich P, Constantinides PP, Wasan KM.	2009	Protonated nanostructured aluminosilicate (NSAS) reduces plasma cholesterol concentrations and atherosclerotic lesions in Apolipoprotein E deficient mice fed a high cholesterol and high fat diet. ; Protonated nanostructured aluminosilicate (NSAS) reduces plasma cholesterol concentrations and atherosclerotic lesions in Apolipoprotein E deficient mice fed a high cholesterol and high fat diet.	Lipids Health Dis. 2009 Jul 28;8:30	No	An investigation to assess the effect of chronic administration of protonated nanostructured aluminosilicate (NSAS) on the plasma cholesterol levels and development of atherosclerotic lesions in Apolipoprotein deficient mice.	Not relevant, protonated nanostructured aluminosilicate (NSAS) used not kaolin.
Spotti M, Fracchiolla ML, Arioli F, Caloni F, Pompa G.	2005	Aflatoxin B1 binding to sorbents in bovine ruminal fluid.	Vet Res Commun. 2005 Aug;29(6):507-15.	No	In vitro experiments to develop a rapid and cheap model using ruminal fluid to assess the ability of sorbent materials to bind aflatoxin B1 (AFB1). Seven sorbents (hydrated sodium calcium aluminosilicate; clinoptilolite; zeolite; two types of bentonite; sepiolite; and PHIL 75), commonly added to bovine diets were incubated in water and ruminal fluid in the presence of AFB1.	Not relevant, bentonite used.

Authors	Year	Title	Source (Journal, volume, pages)	Fulfils data requirement?	Comments	Discussion on relevance
Totsuka Y, Higuchi T, Imai T, Nishikawa A, Nohmi T, Kato T, Masuda S, Kinae N, Hiyoshi K, Ogo S, Kawanishi M, Yagi T, Ichinose T, Fukumori N, Watanabe M, Sugimura T, Wakabayashi K.	2009	Genotoxicity of nano/microparticles in in vitro micronuclei in vivo comet and mutation assay systems. ; Genotoxicity of nano/microparticles in in vitro micronuclei in vivo comet and mutation assay systems.	Part Fibre Toxicol. 2009 Sep 3;6:23.	No	An examination of the effects manufactured nano or /microparticles of C60, CB and kaolin, in an in vitro micronuclei (MN) test. DNA damage and mutations were analysed by in vivo assay systems using transgenic mice which were intratracheally instilled with single or multiple doses.	Not relevant, they used manufactured nano/micro particles that are unlikely to be representative of normal kaolin.
Türkez H, Şişman T.	2007	Anti-genotoxic effect of hydrated sodium calcium aluminosilicate on genotoxicity to human lymphocytes induced by aflatoxin B1.	Toxicol Ind Health. 2007 Mar;23(2):83-9.	No	The anti-genotoxic potential of hydrated sodium calcium aluminosilicate (HSCAS) was investigated using sister chromatid exchanges (SCEs) induced by aflatoxin B1 (AFB1) as genotoxic endpoint in human lymphocytes.	Not relevant, hydrated sodium calcium aluminosilicate (HSCAS) used.
Voinot F, Fischer C, Bœuf A, Schmidt C, Delval-Dubois V, Reichardt F, Liewig N, Chaumande B, Ehret-Sabatier L, Lignot JH, Angel F.	2012	Effects of controlled ingestion of kaolinite (5%) on food intake gut morphology and in vitro motility in rats. ; Effects of controlled ingestion of kaolinite (5%) on food intake gut morphology and in vitro motility in rats.	Fundam Clin Pharmacol. 2012 Oct;26(5):565-76.	No	The study was designed to investigate the effects of controlled kaolinite ingestion on food intake, gut morphology and in vitro motility in rats.	Not relevant as data are essentially already in the public domain i.e. kaolinite effects on gut motility.
Voinot F, Fischer C, Schmidt C, Ehret-Sabatier L, Angel F.	2014	Controlled ingestion of kaolinite (5%) modulates enteric nitrergic innervation in rats.	Fundam Clin Pharmacol. 2014 Aug;28(4):405-13.	No	Gastric emptying and intestinal transit have been shown to be regulated by nitric oxide, the effect of an imposed ingestion of kaolinite on enteric nitrergic innervation was determined. No clear conclusions were reached.	Not relevant, paper describes the effect of ingestion of kaolinite on enteric nitrergic innervation. The data are too speculative.
Yanagisawa R, Takano H, Ichinose T, Mizushima K, Nishikawa M, Mori I, Inoue K,	2007	Gene expression analysis of murine lungs following pulmonary exposure to Asian sand dust particles.	Exp Biol Med (Maywood). 2007 Sep;232(8):1109-18.	No	The examination of the effects of Asian sand dust particles on gene expression in the murine lung using microarray analysis.	Not relevant, kaolin not specifically tested.

Authors	Year	Title	Source (Journal, volume, pages)	Fulfils data requirement?	Comments	Discussion on relevance
Sadakane K, Yoshikawa T.						
Yiannikouris A1, Kettunen H, Apajalahti J, Pennala E, Moran CA.	2013	Comparison of the sequestering properties of yeast cell wall extract and hydrated sodium calcium aluminosilicate in three in vitro models accounting for the animal physiological bioavailability of zearalenone.	Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2013;30(9):1641-50	No	The sequestration/inactivation of the oestrogenic mycotoxin zearalenone (ZEA) by two adsorbents – yeast cell wall extract (YCW) and hydrated sodium calcium aluminosilicate (HSCAS) was studied. HSCAS was an effective sequestering agent,	Not relevant, hydrated sodium calcium aluminosilicate (HSCAS) used.
Zhang Y, Long M, Huang P, Yang H, Chang S, Hu Y, Tang A, Mao L	2016	Emerging integrated nanoclay-facilitated drug delivery system for papillary thyroid cancer therapy.	Sci Rep. 2016 Sep 12;6:33335.	No	Investigation of nanoclay incorporation into dual functional drug delivery systems to promote efficiency in drug delivery and reduce the toxicity of doxorubicin used for thyroid cancer treatment.	Not relevant because nano-clay was used - methoxy-intercalated kaolinite - as a drug delivery system.

Appendix 1 - Processing resources search terms (only Mammalian Toxicology is included in this section)

Absorption	**EC50**	**Hazard**	**Malformation**	**Occupational**	**Sub chronic**
Accidental poisoning	**Endocrine**	**Hazardous**	**Maternal**	**Operator**	**Sub cutaneous**
Acute	**Endocrine disrupting**	**Health**	**Mechanism**	**Oral**	**Sub lethal**
Acute toxicity	**Endocrine disruption**	**Immune system**	**Mechanistic**	**Phototoxicity**	**Sub-chronic**
Adverse	**Endocrine disruptor**	**Immunotoxicity**	**Medical**	**Poison**	**Sub-cutaneous**
Allergic	**Epidemiological**	**Inhalation**	**Metabolic**	**Poisoning**	**Sub-lethal**
Bystander	**Epidemiology**	**Inhibition**	**Metabolism**	**Reproduction toxicity**	**Toxic**
Cancer	**Excretion**	**Intravenous**	**Metabolite**	**Reproductive toxicity**	**Toxicity**
Carcinogen	**Exposure**	**Irritation**	**Mortality**	**Resident**	**Toxicokinetic**
Carcinogenicity	**Fertility**	**LC50**	**Multi-generational**	**Risk assessment**	**Toxicological**
Chronic	**Fetus**	**LD50**	**Neurotoxic**	**Sensitisation**	**Tumor**
Corrosion	**Foetus**	**Lethal**	**Neurotoxicity**	**Short term toxicity**	**Tumors**
Dermal	**Gavage**	**Lethality**	**No observed adverse**	**Side effect**	**Tumour**
Developmental	**Generational**	**Lethally**	**effect - NOEL**	**Side effectsSub-acute**	**Tumours**
Diet	**Genotoxicity**	**LOAEL**	**No observed effect**	**Sub acute**	**Worker**
Dietary		**LOEC**	**NOAEC**		
Distribution		**LOEL**	**NOAEL**		
			NOEC		

APPENDIX IV: LITERATURE DATA BY SOKA

(summary report as submitted by the applicant)

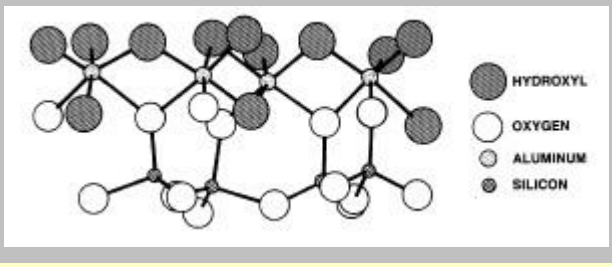
- **Introduction**

ISO-common name:	Kaolin
Synonym:	Aluminium Silicate
Chemical name (IUPAC):	Not available
Chemical name (CAS):	Kaolin
CAS No:	1332-58-7
CIMAP No:	841
EC No:	310-194-1 (E559)

Empirical formula: Hydrous aluminium silicate: Al4Si4O10 (OH)8

Calcined aluminium silicate: Al4Si4O14

Structural formula:



Article 8(5) of Regulation (EC) No 1107/2009 requires applicants submitting dossiers for approval and renewal of active substances to provide relevant scientific peer reviewed open literature. This summary of scientific peer reviewed open literature conforms to EFSA guidance "Submission of scientific peer reviewed open literature under Regulation (EC) No 1107/2009, EFSA Journal 2011; 9(2):2092".

Peer reviewed open literature containing data and analysis dealing with the side effects on health, the environment, and non-target species for common name. The data published within the last ten years before the date of the submission of Aluminium Silicate renewal dossier were reviewed for this document. The document contains the search criteria and results of those searches of "scientific peer-reviewed open literature" performed under Regulation (EC) No 1107/2009 for Aluminium Silicate.

- **Relevance criteria**

Peer reviewed open literature relevant to the dossier may satisfy or partially satisfy data requirements as set out in Regulation (EC) No 1107/2009. The relevance criteria chosen for the selection of peer reviewed scientific open literature is consistent with the OECD guidance and does not restrict the selection of literature (Table 1). The relevance criteria guide the selection of literature dealing with the side effects on health, environment and non-target species for Aluminium Silicate. Non-Good Laboratory Practice studies in open literature may be considered relevant if the design and execution of the study is consistent with generally accepted scientific practice and guidelines. Clearly non-relevant studies are excluded.

Table 1: Criteria for relevance

Data requirement(s) Indicated by the correspondent data point number(s) as identified in Commission Regulation (EU) No 283/2013	Criteria for relevance
All data points	1. The test system, target crop, or species are prescribed by regulation (EC) No 1107/2009 or the relevance is explained if not standard.
	2. Well identified test material, including its purity and impurity profile is described
	3. Study design and/or execution are consistent with relevant study guidelines
	4. The endpoint is relevant to an EU data point as prescribed by Commission Regulation (EU) No 283/2013 and No 284/2013
Toxicological and metabolism studies (CA 5)	5. Description of the observations, examinations, analysis performed, or necropsy are well described.
	6. The conditions of exposure should be from legally registered use of the product
Residues in or on treated products, food and feed (CA 6)	7. The application methods complies with Good Agriculture Practice (GAP)
	8. Appropriate in life/processing conditions are used and/or are well described
Fate and behaviour in the environment (CA 7)	9. The model is appropriate for European regulatory requirements
	10. The input parameters selection is appropriate based on European regulatory requirements
	11. The pedoclimatic conditions are appropriate
Ecotoxicological studies (CA 8)	12. A relevant route of exposure is presented

- **Search criteria**

Reasonable effort was taken to locate all sources of relevant peer reviewed open literature concentrated on comprehensive databases containing worldwide coverage of biology, chemistry, biomedical, agricultural and environmental fields. The search ranged up to 10 years and within 6 months of the submission date of the renewal dossier for Aluminium silicate. The initial search is a single concept search capturing all data points using search terms and synonyms for the active substance. If a large number of search results are returned from the single concept search making assessment for relevance impractical, a separate, focused search is conducted for grouped data points.

Table 2 to Table 6 list the literature search details for the active substance: Aluminium Silicate.

Table 2: Details of literature search for Aluminium Silicate

Details of the searches (Active substance only)			
Database	**Database 1: PubMed**	**Database 2: PubAg**	**Database 3: Agricola and Article citation database (ACD)**
Justification for choosing the source	PubMed is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics.	A bibliographic database containing selective worldwide coverage of agriculture and related fields. (4.2+ million records)	
Date of the search	January 15th, 2018	January 15th, 2018	January 15th, 2018
Date span of the search	2008-2018	2008-2018	2008-2018
Search strategies used for this data requirement	1. Aluminium silicate "aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]	1. Aluminium silicate	1. Aluminium silicate keyword anywhere/ all of these
	Total number of records retrieved: 15277	Total number of records retrieved: 44	Agricola: 0 / ACD: 43
	2. Time window of the literature search: 2008-2018 ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])	2. Time window of the literature search: 2008-2018	2. Time window of the literature search: 2008-2018
	Total number of records retrieved: 7670	Total number of records retrieved: 4	Agricola: 0 / ACD: 30
	3. CAS number: 1332-58-7 ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])		

	Total number of records retrieved: 653
	Total number of summary retrieved: 687

Table 3: Details of literature search for Aluminium Silicate and toxicological and metabolism studies (CA 5)

Details of the searches: Toxicological and metabolism studies (CA 5)		
Data requirement(s)	**Database**	**Database 1: PubMed**
Toxicological and metabolism studies (CA 5)	Justification for choosing the source	PubMed is a free search engine accessing primarily the MEDLINE database of references and abstracts on life sciences and biomedical topics.
	Date of the search	January 15th, 2018
	Date span of the search	2008-2018
	Search strategies used for this data requirement	4. 1-3 Effects on health ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (, effects[All Fields] AND ("health"[MeSH Terms] OR "health"[All Fields])) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 35 After removing duplicate: 35
		5. 1-3 and Toxic ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND , toxic[All Fields] AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 14 After removing duplicate:13
		6. 1-3 and acute toxicity ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (, acute[All Fields] AND ("toxicity"[Subheading] OR "toxicity"[All Fields])) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 5 After removing duplicate: 4

Details of the searches: Toxicological and metabolism studies (CA 5)		
Data requirement(s)	**Database**	**Database 1: PubMed**
	Search strategies used for this data requirement	7. 1-3 and oral toxicity ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("toxicity"[Subheading] OR "toxicity"[All Fields])) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 3 After removing duplicate: 1
		8. 1-3 and dermal toxicity ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (, dermal[All Fields] AND ("toxicity"[Subheading] OR "toxicity"[All Fields])) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 0
		9. 1-3 and inhalation toxicity ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (("inhalation"[MeSH Terms] OR "inhalation"[All Fields]) AND ("toxicity"[Subheading] OR "toxicity"[All Fields])) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 3 After removing duplicate: 1
		10. 1-3 and skin irritation ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (("skin"[MeSH Terms] OR "skin"[All Fields]) AND irritation[All Fields]) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 0

Details of the searches: Toxicological and metabolism studies (CA 5)		
Data requirement(s)	**Database**	**Database 1: PubMed**
	Search strategies used for this data requirement	11. 1-3 and eye irritation ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (("eye"[MeSH Terms] OR "eye"[All Fields]) AND irritation[All Fields]) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 0
		12. 1-3 and skin sensitisation ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (("skin"[MeSH Terms] OR "skin"[All Fields]) AND sensitisation[All Fields]) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 0
		13. 1-3 and dermal absorption ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (, dermal[All Fields] AND ("absorption"[MeSH Terms] OR "absorption"[All Fields])) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 0
		14. 1-3 and operator exposure ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (, operator[All Fields] AND exposure[All Fields]) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 0
		15. 1-3 and worker exposure ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (, worker[All Fields] AND exposure[All Fields]) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 0

Details of the searches: Toxicological and metabolism studies (CA 5)		
Data requirement(s)	**Database**	**Database 1: PubMed**
	Search strategies used for this data requirement	16. 1-3 and toxicological studies ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND (, toxicological[All Fields] AND ("Studies"[Journal] OR "Stud Inst Divi Thomae"[Journal] OR "Brigham Young Univ Stud"[Journal] OR "studies"[All Fields])) AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 1 After removing duplicate: 0
		17. 1-3 and exposure ("aluminum silicates"[MeSH Terms] OR ("aluminum"[All Fields] AND "silicates"[All Fields]) OR "aluminum silicates"[All Fields] OR ("aluminium"[All Fields] AND "silicate"[All Fields]) OR "aluminium silicate"[All Fields]) AND "1332-58-7"[All Fields] AND , exposure[All Fields] AND ("2008/01/19"[PDat] : "2018/01/15"[PDat])
		Total number of records retrieved: 27 After removing duplicate: 20
	Total number of summary records retrieved after removing duplicates: 74	

- **Relevant study selection -results of the selection process**

Obviously non-relevant studies in open literature search were excluded by applying the relevance criteria previously defined in Table 1 of this document. A total of 269 summary records were reviewed, of these 256 were not relevant. When the summary records did not contain sufficient information to assess relevance, full text documents were reviewed in detail for relevance according to the previously defined criteria. After reviewing full text documents of potentially relevant studies, 13 were excluded from further consideration. No relevant studies has been selected for inclusion in the dossier. The Figure 1 summarized the process for selecting studies to be included in the dossier.

Table 7 summarizes the results of the selection process including the number of summary records and full text documents assessed **for toxicological and metabolism studies**.

Table 7: Results of the selection process for toxicological and metabolism studies (CA 5)

Data requirement(s) captured in the search	Number
Total number of summary records retrieved after all searches of peer-reviewed literature (excluding duplicates)	74
Number of records excluded from the search results after rapid assessment for relevance	70
Total number of full text documents assessed in detail	4
Number of studies excluded from the dossier after detailed assessment for relevance	3
Number of studies included in the dossier	1

Literature included in the dossier after detailed assessment

No literature included in the renewal dossier of Aluminium Silicate.

Literature excluded after detailed assessment

Obviously non-relevant studies found in the open literature search were excluded by applying the relevance criteria previously defined in Table 1 of this document.

Table 11: Report of all relevant studies excluded from the risk assessment after detailed assessment of full text documents (ordered by author)

Authors	Year	Title	Source	Reasons for not including this study in the dossier
Arnamwong S., Suksabye P., Thiravetyan P.	2016	Using Kaolin in Reduction of Arsenic in Rice Grains: Effect of Different Types of Kaolin, pH and Arsenic Complex	Bulletin of Environmental Contamination Toxicology, 2016 Apr;96(4):556-61	Criteria 1 in table 1

Authors	Year	Title	Source	Reasons for not including this study in the dossier
Bengochea P., Amor F., Saelices R., Hernando S., Budia F., Adán A., Medina P.	2013	Kaolin and copper-based products applications: ecotoxicology on four natural enemies.	Chemosphere, 2013 May;91(8):1189-95	Criteria 4 in table 1
Bostanian N.J., Racette G.	2008	Particle films for managing arthropod pests of apple.	Journal of Economic Entomology, 2008 Feb;101(1):145-50	Criteria 1 in table 1
Dinis L.T., Bernardo S., Conde A., Pimentel D., Ferreira H., Félix L., Gerós H., Correia C.M., Moutinho-Pereira J.	2016	Kaolin exogenous application boosts antioxidant capacity and phenolic content in berries and leaves of grapevine under summer stress	Journal of Plant Physiology, 2016 Feb 1;191:45-53.	Criteria 4 in table 1
Khaleghi E., Arzani K., Moallemi N., Barzegar M.	2015	The efficacy of kaolin particle film on oil quality indices of olive trees (Olea europaea L.) cv 'Zard' grown under warm and semi-arid region of Iran.	Food Chemistry, 2015 Jan 1;166:35-41	Criteria 4 in table 1
Lemoyne P., Vincent C., Gaul S., MacKenzie K.	2008	Kaolin affects blueberry maggot behavior on fruit	Journal of Economic Entomology, 2008 Feb;101(1):118-25	Criteria 1 in table 1
Leskey T.C., Wright S.E., Glenn D.M., Puterka G.J.	2011	Effect of Surround WP on behavior and mortality of apple maggot (Diptera: Tephritidae)	Journal of Economic Entomology, 2010 Apr;103(2):394-401	Criteria 1 in table 1
Lo Verde G., Rizzo R., Barraco G., Lombardo A.	2010	Effects of kaolin on Ophelimus maskelli (Hymenoptera: Eulophidae) in laboratory and nursery experiments.	Journal of Economic Entomology, 2011 Feb;104(1):180-7	Criteria 1 in table 1
Maisanaba S., Pichardo S., Puerto M., Gutiérrez-Praena D., Cameán A.M., Jos A.	2015	Toxicological evaluation of clay minerals and derived nanocomposites: a review.	Environmental Research, 2015 Apr;138:233-54	Criteria 1 in table 1
Ou C., Du X., Shellie K., Ross C., Qian M.C.	2010	Volatile compounds and sensory attributes of wine from Cv. Merlot (Vitis vinifera L.) grown under differential levels of water deficit with or without a kaolinbased, foliar reflectant particle film.	Journal of Agricultural and Food Chemistry, 2010 Dec 22;58(24):12890-8	Criteria 4 in table 1
Pease C.E., López-Olguín J.F., PérezMoreno I., MarcoMancebón V.	2016	Effects of Kaolin on Lobesia botrana (Lepidoptera: Tortricidae) and Its Compatibility With the Natural Enemy, Trichogramma cacoeciae (Hymenoptera: Trichogrammatidae)	Journal of Economic Entomology, 2016 Apr;109(2):740-5	Criteria 1 in table 1

Authors	Year	Title	Source	Reasons for not including this study in the dossier
Song J., Shellie K.C., Wang H., Qian M.C.	2012	Influence of deficit irrigation and kaolin particle film on grape composition and volatile compounds in Merlot grape (Vitis vinifera L.)	Food Chemistry, 2012 Sep 15;134(2):841-50	Criteria 4 in table 1
Tacoli F., Pavan F., Cargnus E., Tilatti E., Pozzebon A., Zandigiacomo P.	2017	Efficacy and Mode of Action of Kaolin in the Control of Empoasca vitis and Zygina rhamni (Hemiptera: Cicadellidae) in Vineyards	Journal of Economic Entomology, 2017 Jun 1;110(3):1164-1178	Criteria 4 in table 1

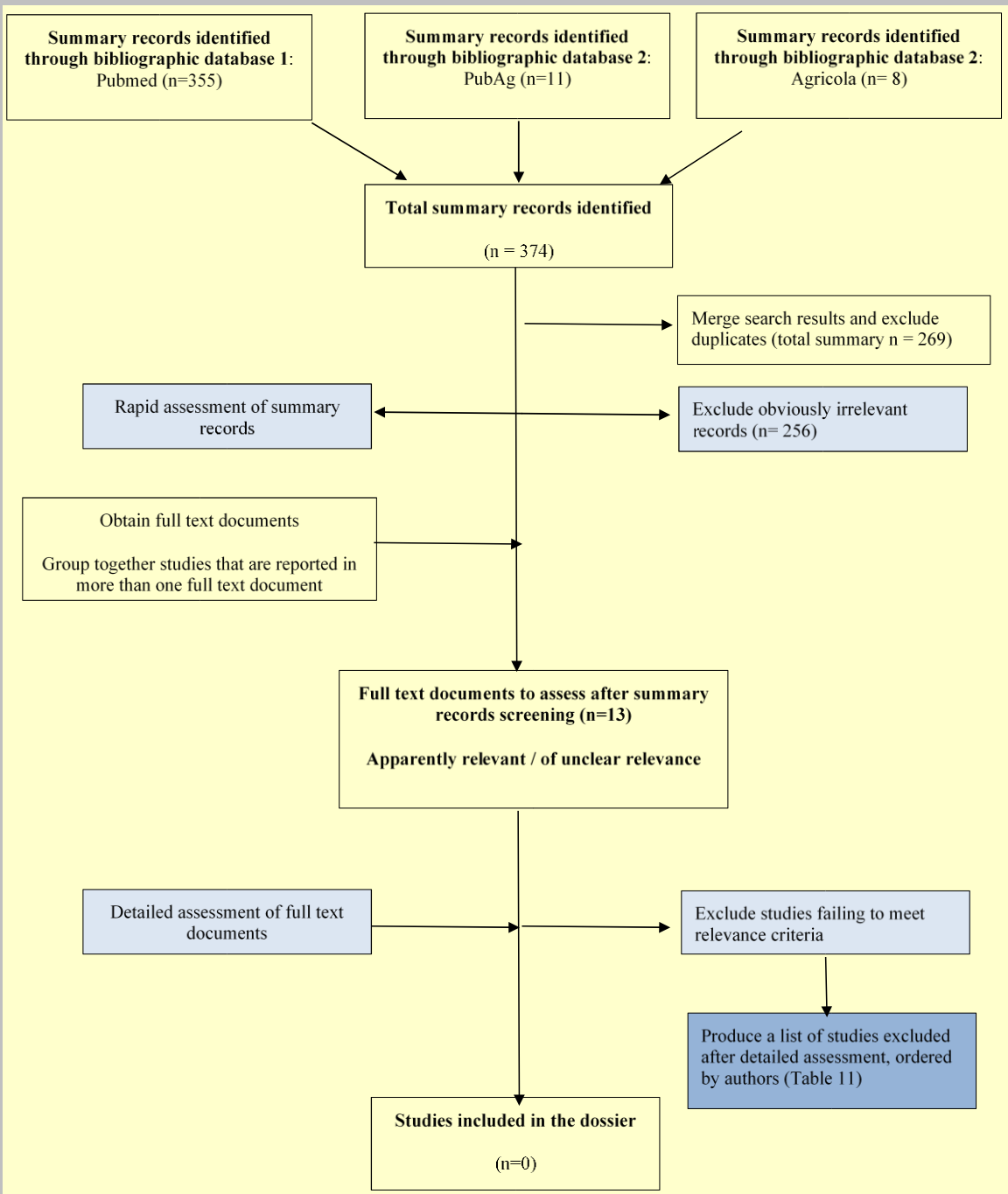


Figure 1: Process for selecting studies to be included in the dossier