Aluminium Silicate

DOCUMENT M-CA, Section 5

TOXICOLOGICAL AND METABOLISM STUDIES ON THE ACTIVE SUBSTANCE

Annex to EU Regulation 283/2013

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Version history[1]

Date	Data points containing amendments or additions and brief description	Document identifier and version number
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[1] It is suggested that applicants adopt a similar approach to showing revisions and version history as outlined in SANCO/10180/2013 Chapter 4 How to revise an Assessment Report

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CA 5 TOXICOLOGICAL AND METABOLISM STUDIES ON THE ACTIVE SUBSTANCE

Introduction

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".

This document contains new summaries of studies and information which were not available at the time of the first Annex I inclusion of aluminium silicate (kaolin), and were therefore not evaluated during the first EU review. To facilitate discrimination between new and original study information, the original information is written in grey shaded text. Studies submitted by the notifier for the first Annex I inclusion are contained in the Monograph, its Addenda and in the original dossier.

Relevance of the test material used in the toxicity dossier

Kaolin is a natural inorganic material, a clay mineral, mined throughout the world. Technical specifications and toxicological studies presented in the Aluminium Silicate (kaolin) Registration dossier submitted by Engelhard Technologies GmbH, transferred to BASF Corporation and later to Tessenderlo Chemie N. V. refer to aluminium silicate extracted from the ore available at McIntyre Plant (BASF Corporation), 1277 Dedrik, McIntyre, Georgia 31054, USA.

Transfer of the Dossier from Engelhard Technologies GmbH arose when BASF Corporation acquired the assets of Engelhard Corporation in the USA and in Europe; these assets included the raw kaolin production and transformation sites mentioned in the dossier, as well as the beneficiation process, quality control lines and product specifications, which remained unchanged. When BASF Corporation divested the business associated with aluminium silicate as a plant

protection product (the "Surround Business"), there were no changes in the technical material specifications since the quality of technical aluminium silicate is critical to the efficacy of the finished product. Therefore, the technical material used in toxicological studies presented in the dossier is similar to that for which technical specifications have been presented.

Unlike synthetic chemicals, where the exact manufacturing plant and precise route of synthesis is critical in determining the impurity profile of a compound, beneficiation of natural mineral products is a process of starting with a broader mix of minerals and removing impurities to arrive at the final high purity. Raw kaolin contains mineral impurities (mica, feldspar, quartz, etc…). Beneficiation refers to the removal of these impurities, thus resulting in kaolin of >99.98% purity. Pure kaolin may still contain trace metals incorporated in it crystal matrix as substitutes for Aluminium and Silica. However, these metals are not made bioavailable through natural degradation mechanisms.

Aluminium silicate referenced in the submitted Registration dossier undergoes calcination as part of the beneficiation process. Calcination takes place at 1100°C and at that temperature organic impurities of toxicological significance such as dioxins, furans, dioxin-like and non-dioxin-like PCBs are completely destroyed. This is confirmed in the batch analysis data provided in the technical specifications dossier.

None of the studies provided in the Registration dossier highlighted any toxicological concerns based on systemic toxicity that could be caused by impurities present in the technical material tested. Since the raw material from which aluminium silicate is obtained comes from the same source and undergoes the same treatment as the material used in the toxicological studies provided in the registration dossier, it is reasonable to consider that results obtained from toxicological studies provided in the Registration dossier apply to technical grade aluminium silicate for which technical specifications are provided.

CA 5.1 Studies on Absorption, Distribution, Metabolism and Excretion in Mammals

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

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[1], has led Tessenderlo Group N.V. to request a waiver for ADME studies.

CA 5.1.1 Absorption, distribution, metabolism and excretion by oral exposure

Not applicable, see CA 5.1 above.

CA 5.1.2 Absorption, distribution, metabolism and excretion by other routes

Considering the information in CA 5.1 above, ADME by other routes is waived from this dossier.

CA 5.2 Acute Toxicity

CA 5.2.1 Acute Oral Toxicity

Report:	KCA 5.2.1/01, [redacted] 1997a
Title:	Satintone® 5HB, Lot #10146 "Calcined Kaolin" - Acute Oral Toxicity Limit Test
Report No:	4903
Guidelines:	40 CFR 158, Guideline #81-1 – FIFRA
GLP:	Yes

Executive Summary

In an acute oral toxicity test, Satintone® 5HB, as manufactured, 100% kaolin, was administered as a 36% w/w suspension in distilled water (5000 mg/kg bw) by oral gavage to five male and five female Sprague-Dawley albino rats. The test animals were observed for 14 days following administration of the test substance.

Oral LD_{50}:	Males	=	> 5000 mg/kg bw
	Females	=	> 5000 mg/kg bw
	Combined	=	> 5000 mg/kg bw

Test material is not toxic to rats following exposure by the oral route. No clinical signs were observed, and all rats appeared active and healthy throughout the study. There were no signs of gross toxicity, adverse pharmacological effects or abnormal behaviour. Gross necropsy findings at terminal sacrifice were generally unremarkable. Apart from red lung discolouration consistent with euthanasia by CO_2 inhalation, all tissues and organs appeared normal.
Based on this study, test material does not warrant classification as harmful or toxic when administered orally.

I MATERIALS AND METHODS

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

A. MATERIALS

1. Test Material:	Satintone® 5HB
Description:	White powder
Lot/Batch #:	10146
Purity:	Not stated
Stability of test component:	Stable
2. Vehicle and/or positive control:	distilled water
3. Test animals –	
Species:	Rat
Strain:	Sprague-Dawley derived, albino
Age:	Young adults, male and female
Weight at dosing:	202 – 221g males, 165 – 180 g females
Source:	Ace Animals, Inc. Boyertown, PA
Acclimation:	7 days
Diet:	Purina Rodent Chow (#5012) *ad libitum*
Water:	Filtered tap water, *ad libitum*
Housing:	Animals were individually housed in stainless steel suspended cages
Environmental conditions –	
Temperature:	20-23ºC
Humidity:	Not specified
Air changes:	Not specified
Photoperiod:	12-hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates: 17-31 December 1996

2. Animal assignment and treatment

Animals were fasted for approximately 19 hours prior to selection. Ten (five males, five females) healthy rats were selected for test. Individual doses were calculated, and a dose of 5000 mg/kg bw was administered to each rat via a stainless-steel ball-tipped gavage needle attached to an appropriate syringe. Test substance was administered as a 36% suspension in distilled water. Animals were observed for signs of gross toxicity and behaviour changes at 1 and 3 hours post dosing and at least once daily thereafter for 14 days. Bodyweights were recorded at day 0 (prior to dosing) and again at day 7 and 14. At day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSIONS

A. MORTALITY

Details are provided in table 5.2.1-1. No mortality occurred at 5000 mg/kg bw, the only dose level tested.

Table 5.2.1-1. Doses, mortality / animals treated

Dose (mg/kg bw)	Males	Females	Combined
5000	0/5	0/5	0/10

Oral LD_{50}: Males = > 5000 mg/kg bw
Females = > 5000 mg/kg bw
Combined = > 5000 mg/kg bw

B. CLINICAL OBSERVATIONS

All animals appeared active and healthy throughout the study.

C. BODYWEIGHT

All animals had gained bodyweight 7 and 14 days following dosing.

D. NECROPSY

Gross necropsy findings at termination sacrifice were generally unremarkable. Apart from red discolouration consistent with euthanasia by CO_2 inhalation, all tissues and organs appeared normal.

E. DEFICIENCIES

None.

III. CONCLUSIONS

The acute oral LD_{50} for Satintone® 5HB 99.99% kaolin mineral is greater than 5000 mg/kg bw for male and female rats. The preparation does not warrant classification as being toxic or harmful based on its acute oral toxicity.

Report:	KCA 5.2.1/02, [redacted] 1997b
Title:	M-96-018, Lot #08145 - Acute Oral Toxicity Limit Test.
Report No:	5003
Guidelines:	40 CFR 158, Guideline #81-1 – FIFRA

GLP:	Yes

Executive Summary

In an acute oral toxicity test, M-96-018, as manufactured, 98.8% kaolin, was administered as a 30% w/w suspension in corn oil (5000 mg/kg bw) by oral gavage to five male and five female Sprague-Dawley albino rats. Due to the volume of the dose (15.22 ml/kg), the test material was administered in two approximately equal portions, two hours apart. The test animals were observed for 14 days following administration of the test substance.

Oral LD_{50}:	Males	=	> 5000 mg/kg bw
	Females	=	> 5000 mg/kg bw
	Combined	=	> 5000 mg/kg bw

Test material is not toxic to rats following exposure by the oral route. No clinical signs were observed, and all rats appeared active and healthy throughout the study. There were no signs of gross toxicity, adverse pharmacological effects or abnormal behaviour. Gross necropsy findings at terminal sacrifice were generally unremarkable. Apart from red lung discolouration consistent with euthanasia by CO_2 inhalation, all tissues and organs appeared normal. Based on this study, test material does not warrant classification as harmful or toxic when administered orally.

I MATERIALS AND METHODS

A. MATERIALS

1. Test Material:	M-96-018
Description:	White powder
Lot/Batch #:	08145
Purity:	Not stated, 98.8% kaolin 1.2% siloxane
Stability of test component:	Stable
2. Vehicle and/or positive control:	Corn oil
3. Test animals –	
Species:	Rat
Strain:	Sprague-Dawley derived, albino
Age:	Young adults, male and female
Weight at dosing:	175-215 g males, 168-173 g females
Source:	Ace Animals, Inc. Boyertown, PA
Acclimation:	7 days
Diet:	Purina Rodent Chow (#5012) *ad libitum*
Water:	Filtered tap water, *ad libitum*
Housing:	Animals were individually housed in stainless steel suspended cages

Environmental conditions –

Temperature:	20-22ºC
Humidity:	Not specified
Air changes:	Not specified
Photoperiod:	12-hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates: 4-18 February 1997

2. Animal assignment and treatment

Animals were fasted for approximately 20 hours prior to selection. Ten (five males, five females) healthy rats were selected for test. Individual doses were calculated, and a dose of 5000 mg/kg bw was administered to each rat via a stainless-steel ball-tipped gavage needle attached to an appropriate syringe. Test substance was administered as a 30% suspension in corn oil. Due to the high volume of test suspension to be administered (15.22 ml/kg), each animal's dose was divided into two approximately equal portions and administered two hours apart.
Animals were observed for signs of gross toxicity and behaviour changes at 1, 2, 3 and 4 hours post dosing and at least once daily thereafter for 14 days. Bodyweights were recorded at day 0 (prior to dosing) and again at day 7 and 14. At day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSIONS

A. MORTALITY

Details are provided in table 5.2.1-2. No mortality occurred at 5000 mg/kg bw, the only dose level tested

Table 5.2.1-2. Doses, mortality / animals treated

Dose (mg/kg bw)	Males	Females	Combined
5000	0/5	0/5	0/10

Oral LD_{50}:	Males	=	> 5000 mg/kg bw
	Females	=	> 5000 mg/kg bw
	Combined	=	> 5000 mg/kg bw

B. CLINICAL OBSERVATIONS

All animals appeared active and healthy throughout the study.

C. BODYWEIGHT

All animals had gained bodyweight 7 and 14 days following dosing.

D. NECROPSY

Gross necropsy findings at termination sacrifice were generally unremarkable. Apart from red discolouration consistent with euthanasia by CO_2 inhalation, all tissues and organs appeared normal.

E. DEFICIENCIES

None.

III. CONCLUSIONS

The acute oral LD_{50} for M-96-018 is greater than 5000 mg/kg bw for male and female rats. The preparation does not warrant classification as being toxic or harmful based on its acute oral toxicity.

CA 5.2.2 Acute Dermal Toxicity

Report:	KCA 5.2.2/01, [redacted] 1997
Title:	Satintone® 5HB, Lot #10146 Acute Dermal Toxicity Limit Test
Report No:	4904
Guidelines:	40 CFR 158, Guideline #81-2 – FIFRA
GLP:	Yes

Executive Summary

In an acute dermal toxicity test, Satintone® 5HB, as manufactured, 100% kaolin, was moistened to a dry paste with distilled water, administered to the closely clipped dorsum of five male and five female Sprague-Dawley albino rats at a dose level of 5000 mg/kg bw, and was covered with an occlusive dressing for 24 hours.

Dermal LD_{50}:	Males	=	> 5000 mg/kg bw
	Females	=	> 5000 mg/kg bw
	Combined	=	> 5000 mg/kg bw

Test material is not toxic to rats following exposure by the dermal route. No clinical signs were observed, and all rats appeared active and healthy throughout the study. There were no signs of gross toxicity, adverse pharmacological effects or abnormal behaviour. Gross necropsy findings at terminal sacrifice were generally unremarkable. Apart from red lung discolouration consistent with euthanasia by CO_2 inhalation, all tissues and organs appeared normal. Based on this study, test material does not warrant classification as harmful or toxic when administered topically.

I MATERIALS AND METHODS

A. MATERIALS

1. Test Material:	Satintone® 5HB
Description:	White powder
Lot/Batch #:	10146
Purity:	Not stated
Stability of test component:	Stable
2. Vehicle and/or positive control:	distilled water
3. Test animals –	
Species:	Rat
Strain:	Sprague-Dawley derived, albino
Age:	Young adults, male and female
Weight at dosing:	232-240g males, 216-238g females
Source:	Ace Animals, Inc. Boyertown, PA
Acclimation:	20 days
Diet:	Purina Rodent Chow (#5012) *ad libitum*
Water:	Filtered tap water, *ad libitum*
Housing:	Animals were individually housed in stainless steel suspended cages
Environmental conditions –	
Temperature:	20-22ºC
Humidity:	Not specified
Air changes:	Not specified
Photoperiod:	12-hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates:	30 December 1996 – 13 January 1997

2. Animal assignment and treatment

On the day prior to application, a group of animals was prepared by clipping the dorsal area and the trunk. After clipping and prior to application, the animals were examined for health, weighed (initial) and the skin checked for any abnormalities. Ten (five males, five females) healthy rats were selected for test. The test substance was moistened to a dry paste by preparing a 50% w/w mixture with distilled water. 5000 mg/kg bw of the paste was applied to a dose area representing approximately 10% of body surface, and maintained for 24 hours with a semi-occlusive bandage. Animals were observed for signs of gross toxicity and behaviour changes at 1 and 3 hours post dosing and at least once daily thereafter for 14 days. Bodyweights were recorded at day 0 (prior to dosing) and again at day 7 and 14. At day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSIONS

A. MORTALITY

Details are provided in table 5.2.2-1. No mortality occurred at 5000 mg/kg bw, the only dose level tested.

Table 5.2.2-1. Doses, mortality / animals treated

Dose (mg/kg bw)	Males	Females	Combined
5000	0/5	0/5	0/10

Dermal LD_{50}: Males = > 5000 mg/kg bw
Females = > 5000 mg/kg bw
Combined = > 5000 mg/kg bw

B. CLINICAL OBSERVATIONS

All animals appeared active and healthy throughout the study.

C. BODYWEIGHT

All animals had gained bodyweight 7 and 14 days following dosing.

D. NECROPSY

Gross necropsy findings at termination sacrifice were generally unremarkable. Apart from red discolouration consistent with euthanasia by CO_2 inhalation, all tissues and organs appeared normal.

E. DEFICIENCIES

None.

III. CONCLUSIONS

The acute dermal LD_{50} for Satintone® 5HB 99.99% kaolin mineral is greater than 5000 mg/kg bw for male and female rats. The preparation does not warrant classification as being toxic or harmful based on its acute oral toxicity.

CA 5.2.3 Acute Inhalation Toxicity

Report:	KCA 5.2.3/01, [redacted] 1997a
Title:	M-97-009, Lot #09255 “Calcined Kaolin”- Acute Inhalation Toxicity Limit Test.

Report No:	5405
Guidelines:	40 CFR 158, Guideline #81-3 – FIFRA
GLP:	Yes

Executive Summary

In an acute inhalation toxicity test, M-97-009, as manufactured, 100% kaolin, was administered as an aerosol suspension (concentration 2.07 mg/l, maximal attainable concentration) for 4 hours and 9 minutes to five male and five female Sprague-Dawley albino rats. The test animals were observed for 14 days following administration of the test substance.

Inhalation LD_{50}:	Males	=	> 2.07 mg/l
	Females	=	> 2.07 mg/l
	Combined	=	> 2.07 mg/l

Test material is not toxic to rats following inhalation exposure. During the initial 2.5 hours of exposure, animals exhibited nasal and ocular discharge, irregular respiration, hunched posture. All rats recovered from these symptoms within 17 hours and appeared active and healthy during the reminder of the study. There were no signs of gross toxicity, adverse pharmacological effects or abnormal behaviour. Gross necropsy findings at terminal sacrifice were generally unremarkable. Apart from red lung discolouration consistent with euthanasia by CO_2 inhalation, all tissues and organs appeared normal. Based on this study, test material does not warrant classification as toxic or harmful by inhalation.

I MATERIALS AND METHODS

A. MATERIALS

1. Test Material: M-97-009
   - Description: White powder
   - Lot/Batch #: 09255
   - Purity: Not stated
   - Stability of test component: Stable

2. Vehicle and/or positive control: None

3. Test animals –
   - Species: Rat
   - Strain: Sprague-Dawley derived, albino
   - Age: Young adults, male and female
   - Weight at dosing: 226-238g males, 197-211g females
   - Source: Ace Animals, Inc. Boyertown, PA
   - Acclimation: 10 days
   - Diet: Purina Rodent Chow (#5012) *ad libitum*
   - Water: Filtered tap water, *ad libitum*

Housing:	Animals were individually housed in stainless steel suspended cages

Environmental conditions –

Temperature:	16-24ºC
Humidity:	Not specified
Air changes:	Not specified
Photoperiod:	12-hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates: 25 July – 8 August 1997

2. Animal assignment and treatment

Ten (five males, five females) healthy rats were selected for test. Animals were observed for signs of gross toxicity and behaviour changes before exposure, at least every 30 minutes during the first 2.5 hours during exposure, upon removal from the chamber and at least once daily thereafter for 14 days. Bodyweights were recorded at day 0 (prior to dosing) and again at day 7 and 14. At day 14, surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

3. Generation of the test atmosphere / chamber description

A rectangular whole-body Perspex chamber with a volume of 100 l operated under slight negative pressure was used. Test material was ground in a ball mill for 24 hours to achieve a mass median aerodynamic diameter of 2.5 µm. Chamber concentrations were determined by collecting samples on pre-weighed Whatman GF/B filter papers, measuring the mass of sample collected and dividing by the total volume of air sampled. The test atmosphere concentration was 2.07 mg/l

4. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSIONS

A. MORTALITY

Details are provided in table 5.2.3-1. No mortality occurred at 2.07 mg/l, the only concentration level tested

Table 5.2.3-1. Doses, mortality / animals treated

Dose (mg/l)	Males	Females	Combined
2.07	0/5	0/5	0/10

Oral LD_{50}: Males = > 2.07 mg/l
Females = > 2.07 mg/l

Combined = > 2.07 mg/l

B. CLINICAL OBSERVATIONS

During exposure, animals exhibited ocular and nasal discharge, irregular respiration and hunched posture. All animals appeared active and healthy throughout the study.

C. BODYWEIGHT

All animals survived exposure, gained bodyweight over the 14-day observation period.

D. NECROPSY

Gross necropsy findings at terminal sacrifice revealed red foci on the surface of the lungs of one female. Apart from red lung discolouration consistent with CO_2 inhalation, all other tissues and organs appeared normal.

E. DEFICIENCIES

None.

III. CONCLUSIONS

The median lethal chamber concentration for four hours exposure (LC_{50}, 4 hour) for M-97-009, Lot #09255, 100% calcined kaolin is greater than 2.07 mg per litre of air. The preparation does not warrant classification as being toxic or harmful based on its acute inhalation toxicity.

Report:	KCA 5.2.3/02, [redacted] 1997b
Title:	M-96-018 - Acute Inhalation Toxicity Limit Test.
Report No:	5424
Guidelines:	40 CFR 158, Guideline #81-3 – FIFRA
GLP:	Yes

Executive Summary

In an acute inhalation toxicity test, M-96-018 as manufactured, 98.8% kaolin, ,1.2% siloxane, was administered as an aerosol suspension (concentration 2.18 mg/l, maximal attainable concentration) for 4 hours to five male and five female Sprague-Dawley albino rats. The test animals were observed for 14 days following administration of the test substance.

Inhalation LD_{50}:	Males	=	> 2.18 mg/l
	Females	=	> 2.18 mg/l
	Combined	=	> 2.18 mg/l

Test material is not toxic to rats following inhalation exposure. During the initial 1 hour of exposure, animals exhibited nasal and ocular discharge, hypoactivity, hunched posture. All rats

recovered from these symptoms within 17 hours and appeared active and healthy during the reminder of the study. There were no signs of gross toxicity, adverse pharmacological effects or abnormal behaviour. Gross necropsy findings at terminal sacrifice were generally unremarkable. Apart from red lung discolouration consistent with euthanasia by CO_2 inhalation, all tissues and organs appeared normal. Based on this study, test material does not warrant classification as toxic or harmful by inhalation.

I MATERIALS AND METHODS

A. MATERIALS

1. Test Material:	M-96-018
Description:	White powder
Lot/Batch #:	Not stated
Purity:	98.8% kaolin 1.2% siloxane
Stability of test component:	Stable

2. Vehicle and/or positive control:	None

3. Test animals –	
Species:	Rat
Strain:	Sprague-Dawley derived, albino
Age:	Young adults, male and female
Weight at dosing:	214-244g males, 185-203g females
Source:	Ace Animals, Inc. Boyertown, PA
Acclimation:	9 days
Diet:	Purina Rodent Chow (#5012) *ad libitum*
Water:	Filtered tap water, *ad libitum*
Housing:	Animals were individually housed in stainless steel suspended cages

Environmental conditions –	
Temperature:	17-22ºC
Humidity:	Not specified
Air changes:	Not specified
Photoperiod:	12-hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates:	31 July – 14 August 1997

2. Animal assignment and treatment

Ten (five males, five females) healthy rats were selected for test. Animals were observed for signs of gross toxicity and behaviour changes before exposure, at least every 30 minutes during the first hour during exposure, upon removal from the chamber and at least once daily thereafter for 14 days. Bodyweights were recorded at day 0 (prior to dosing) and again at day 7 and 14. At day 14,

surviving animals were sacrificed and all animals were necropsied and examined for gross pathological changes.

3. Generation of the test atmosphere / chamber description

A rectangular whole-body Perspex chamber with a volume of 100 l operated under slight negative pressure was used. Test material was ground in a ball mill for 24 hours to achieve a mass median aerodynamic diameter of 2.0 µm. Chamber concentrations were determined by collecting samples on pre-weighed Whatman GF/B filter papers, measuring the mass of sample collected and dividing by the total volume of air sampled. The test atmosphere concentration was 2.18 mg/l

4. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSIONS

A. MORTALITY

Details are provided in table 5.2.3-2. No mortality occurred at 2.18 mg/l, the only concentration level tested

Table 5.2.3-2. Doses, mortality / animals treated

Dose (mg/l	Males	Females	Combined
2.18	0/5	0/5	0/10

Oral LD_{50}:	Males	=	> 2.18 mg/l
	Females	=	> 2.18 mg/l
	Combined	=	> 2.18 mg/l

B. CLINICAL OBSERVATIONS

During exposure, animals exhibited ocular and nasal discharge, hypoactivity and hunched posture. All animals appeared active and healthy throughout the study.

C. BODYWEIGHT

All animals survived exposure, gained bodyweight over the 14-day observation period.

D. NECROPSY

Gross necropsy findings at terminal sacrifice were generally unremarkable. Apart from red lung discolouration consistent with CO_2 inhalation, all other tissues and organs appeared normal.

E. DEFICIENCIES

None.

III. CONCLUSIONS

The median lethal chamber concentration for four hours exposure (LC_{50}, 4 hour) for M-96-018, 98.8% calcined kaolin is greater than 2.18 mg per litre of air. The preparation does not warrant classification as being toxic or harmful based on its acute inhalation toxicity.

CA 5.2.4 Skin Irritation

Report:	CA 5.2.4/01, [redacted] 1997
Title:	M-96-018, lot #08145 – Primary Skin Irritation.
Report No:	4906
Guidelines:	40 CFR 158, Guideline #81-5 – FIFRA
GLP:	Yes

Executive Summary

In a primary skin irritation test, M-96-018, as manufactured, 98.8% kaolin, was administered as a dry paste to the skin of six healthy rabbits for 4 hours. The test animals were observed at approximately 1, 24, 48 and 72 hours following administration of the test substance. Irritation was scored according to Draize *et al*[2]. All animals appeared active and healthy throughout the study. There were no signs of gross toxicity, adverse pharmacologic effects or abnormal behaviour. No dermal irritation was noted at any treated site throughout the study. Based on this study, test material does not warrant classification as irritating to skin.

I MATERIALS AND METHODS

A. MATERIALS

1. Test Material:	M-96-018
Description:	White powder
Lot/Batch #:	08145
Purity:	98.8% kaolin
	1.2% polydimethylsiloxane
Stability of test component:	Stable
2. Vehicle and/or positive control:	Distilled water

3. Test animals –

[2] Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390

Species:	Rabbit
Strain:	New Zealand, albino
Age:	Adults, male and female
Weight at dosing:	Not stated
Source:	Davidson's Mill Farm, South Brunswick, NJ
Acclimation:	13 days
Diet:	Pelleted Purina Rabbit Chow (#5326)
Water:	Filtered tap water, *ad libitum*
Housing:	Animals were individually housed in stainless steel suspended cages

Environmental conditions –

Temperature:	17.5-18.5ºC
Humidity:	Not specified
Air changes:	Not specified
Photoperiod:	12-hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates: 19-22 December 1996

2. Animal assignment and treatment

Test substance was moistened to a dry pasted and 0.5 g was applied to the clipped dorsum of six New Zealand albino rabbits (three males and three females). The test substance was kept in place with the aid of an occlusive bandage for four hours. After four hours, the bandage was removed, and residual test substance was removed using water and a clean towel.

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSIONS

A. FINDINGS

Details are provided in table 5.2.4-1. No irritation was observed in any of the treated animals.

Table 5.2.4-1 Irritation indices following application of M-96-018 to the skin of New Zealand rabbits

Animal Number	Type of Response	Score After Removal of Dressings			
		1 Hour	24 Hours	48 Hours	72 Hours
1102 M	Erythema	0	0	0	0
	Oedema	0	0	0	0
1103 F	Erythema	0	0	0	0
	Oedema	0	0	0	0
1104 M	Erythema	0	0	0	0
	Oedema	0	0	0	0
1105 F	Erythema	0	0	0	0
	Oedema	0	0	0	0
1106 M	Erythema	0	0	0	0
	Oedema	0	0	0	0
1107 F	Erythema	0	0	0	0
	Oedema	0	0	0	0

All scores at each of the reading times (24, 48 and 72 hours) for an effect are used for calculating respective mean values. Mean scores over 24, 48 and 72 hours for the six rabbits were:

Erythema: 0.0
Oedema: 0.0

III. CONCLUSIONS

Based on this test, M-96-018 – kaolin, Lot #08145 is classified as non-irritating to the skin.

CA 5.2.5 Eye Irritation

Report:	KCA 5.2.3/01, [redacted] G 1997
Title:	M-96-018, lot #08145 – Primary Eye Irritation.
Report No:	4905
Guidelines:	40 CFR 158, Guideline #81-4 – FIFRA
GLP:	Yes

In a primary eye irritation test, M-96-018, as manufactured, 98.8% kaolin (0.1 ml, approx. 0.04 to 0.05 g) was instilled in the right conjunctival sac of nine healthy rabbits. The other eye served as control. Test substance was rinsed off the eye of three out of the nine rabbits with physiological

saline. Eye irritation was scored according to Draize *et al*[3] at 1, 24, 48 and 72 hours post instillation. All animals appeared active and healthy throughout the study. Apart from the eye irritation noted below, 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 test substance instillation, all treated eyes (rinsed and unrinsed) exhibited conjunctivitis. The incidence and severity of irritation decreased thereafter. All rinsed and unrinsed eyes were free from irritation by 24 and 72 hours respectively. Based on this test, test substance is not irritating to eyes.

I MATERIALS AND METHODS

A. MATERIALS

1. Test Material:	M-96-018
Description:	White powder
Lot/Batch #:	08145
Purity:	not stated. 98.8% kaolin 1.2% polydimethylsiloxane
Stability of test component:	Stable
2. Vehicle and/or positive control:	none
3. Test animals –	
Species:	Rabbit
Strain:	New Zealand, albino
Age:	Adults, female
Weight at dosing:	Not stated
Source:	Davidson's Mill Farm, South Brunswick, NJ
Acclimation:	19 days
Diet:	Pelleted Purina Rabbit Chow (#5326)
Water:	Filtered tap water, *ad libitum*
Housing:	Animals were individually housed in stainless steel suspended cages
Environmental conditions –	
Temperature:	19.5-22ºC
Humidity:	Not specified
Air changes:	Not specified
Photoperiod:	12-hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates:	23-26 December 1996

[3] Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390

2. Animal assignment and treatment

Prior to instillation, both eyes of potential test animals were examined using a fluorescein dye procedure. Only healthy animals without pre-existing ocular lesions were selected for the study. 0.1 ml (approximately 0.04 to 0.05g) of the test substance was instilled in the conjunctival sac of the right eye of each rabbit. The eyelids were then gently held together for about one second. The contralateral eye served as control. In three test animals, the test eye was rinsed with physiological saline (0.9% NaCl) approximately 20-30 seconds after instillation. The test eye of the six remaining test animals remained unrinsed. Scoring took place 1, 24, 48 and 72 hours after instillation. The fluorescein dye procedure was used at 24 hours to verify the absence of corneal damage.

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSIONS

A. FINDINGS

Details are provided in table 5.2.5-1.

Table 5.2.5-1 Incidence, severity and reversibility of irritation

Time Post Instillation	Incidence of Irritation					
	Unrinsed			Rinsed		
	Corneal Opacity	Iritis	Conjunctivitis	Corneal Opacity	Iritis	Conjunctivitis
1 hour	0/6	0/6	6/6	0/3	0/3	3/3
24 hours	0/6	0/6	5/6	0/3	0/3	0/3
48 hours	0/6	0/6	2/6	0/3	0/3	0/3
72 hours	0/6	0/6	0/6	0/3	0/3	0/3

B. FINDINGS – UNRINSED EYES ONLY

Reddening of the conjunctiva was observed in all rabbits one-hour post instillation. After 24 hours, the incidence of irritation in all six rabbits was below the level required for classification of the substance as irritating to the eyes, and by 48 hours, only two rabbits showed slight signs of irritation. All rabbits had fully recovered by 72 hours. No corneal damage or iritis was observed at any time during the observation period.

Individual scores in unrinsed eyes are provided in the table below:

Table 5.2.5-2 Individual scores – Unrinsed eye only

Rabbit No / Sex	Region of eye		1 h	24 h	48 h	72 h
1124	Cornea		0	0[1]	0	0
Female	Iris		0	0	0	0
	Conjunctiva	Redness	3	2	1	0
		Chemosis	1	1	0	0
		Discharge	1	1	0	0
1125	Cornea		0	0[1]	0	0
Female	Iris		0	0	0	0
	Conjunctiva	Redness	2	1	0	0
		Chemosis	0	0	0	0
		Discharge	1	0	0	0
1126	Cornea		0	0[1]	0	0
Female	Iris		0	0	0	0
	Conjunctiva	Redness	2	1	0	0
		Chemosis	1	0	0	0
		Discharge	2	0	0	0
1127	Cornea		0	0[1]	0	0
Female	Iris		0	0	0	0
	Conjunctiva	Redness	2	0	0	0
		Chemosis	1	0	0	0
		Discharge	2	0	0	0
1128	Cornea		0	0[1]	0	0
Female	Iris		0	0	0	0
	Conjunctiva	Redness	3	2	1	0
		Chemosis	1	0	0	0
		Discharge	1	0	0	0
1129	Cornea		0	0[1]	0	0
Female	Iris		0	0	0	0
	Conjunctiva	Redness	2	1	0	0
		Chemosis	0	0	0	0
		Discharge	2	0	0	0

[1]: 2% fluorescein sodium used to verify the absence of corneal opacity

All scores at each reading time (24, 48 and 72 hours) and for an effect were used for calculating the respective mean values. The mean scores for the six animals over 24, 48 and 72 hours were:

Chemosis	:	0.06
Redness of the conjunctiva	:	0.50
Iris lesions	:	0.00
Corneal opacity	:	0.00

III. CONCLUSIONS

Based on this test, M-96-018 – kaolin, Lot #08145 does not warrant classification as irritating to the eye.

Report:	KCA 5.2.5/02, [redacted] 2000
Title:	Surround® WP Crop Protectant - Primary Eye Irritation Study in Rabbits
Report No:	9914
Guidelines:	Health Effects Test Guidelines, OPPTS 870.2400 (1998)
GLP:	Yes

Executive Summary

In a primary eye irritation test, Surround WP Crop Protectant, as manufactured, 95% kaolin (0.1 ml, approx. 0.04 to 0.05 g) was instilled in the right conjunctival sac of 3 healthy rabbits (one male, two females). The other eye served as control. Eye irritation was scored according to Draize *et al*[4] at 1, 24, 48 and 72 hours post instillation. All animals appeared active and healthy throughout the study. Apart from the eye irritation noted below, 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 test substance instillation, all treated eyes (rinsed and unrinsed) exhibited conjunctivitis. The incidence and severity of irritation decreased thereafter. All rinsed and unrinsed eyes were free from irritation by 24 and 72 hours respectively. Based on this test, test substance is not irritating to eyes.

I MATERIALS AND METHODS

A. MATERIALS

1. Test Material: Surround® WP Crop Protectant
   - Description: White powder
   - Lot/Batch #: 02140
   - Purity: 95% kaolin
   - Stability of test component: Stable

2. Vehicle and/or positive control: none

3. Test animals –
   - Species: Rabbit
   - Strain: New Zealand, albino
   - Age: Adults, male and female

[4] Draize, J.H., Woodward, G. and Calvery, H.O. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol. Exp. Ther.* 1944; 82:377-390

Weight at dosing:	Not stated
Source:	Davidson's Mill Farm, South Brunswick, NJ
Acclimation:	14 days
Diet:	Pelleted Purina Rabbit Chow (#5326)
Water:	Filtered tap water, *ad libitum*
Housing:	Animals were individually housed in stainless steel suspended cages

Environmental conditions –

Temperature:	21-23ºC
Humidity:	Not specified
Air changes:	Not specified
Photoperiod:	12-hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates: 17-20 November 2000

2. Animal assignment and treatment

Prior to instillation, both eyes of potential test animals were examined using a fluorescein dye procedure. Only healthy animals without pre-existing ocular lesions were selected for the study. 0.1 ml (approximately 0.04 to 0.05g) of the test substance was instilled in the conjunctival sac of the right eye of each rabbit. The eyelids were then gently held together for about one second. The contralateral eye served as control. Scoring took place 1, 24, 48 and 72 hours after instillation. The fluorescein dye procedure was used at 24 hours to verify the absence of corneal damage.

3. Statistics

The data did not warrant statistical analysis.

II. RESULTS AND DISCUSSIONS

A. FINDINGS

Details are provided in table 5.2.5-3.

Table 5.2.5-3 Incidence, severity and reversibility of irritation

Time Post Instillation	Incidence of Irritation		
	Corneal Opacity	Iritis	Conjunctivitis
1 hour	0/3	0/3	3/3
24 hours	0/3	0/3	2/3
48 hours	0/3	0/3	0/3
72 hours	0/3	0/3	0/3

B. FINDINGS – UNRINSED EYES ONLY

Reddening of the conjunctiva was observed in all rabbits one-hour post instillation. After 24 hours, the incidence of irritation in all three rabbits was below the level required for classification of the substance as irritating to the eyes. All rabbits had fully recovered by 48 hours. No corneal damage or iritis was observed at any time during the observation period.

Individual scores in are provided in table 5.2.5-4

Table 5.2.5-4 Individual scores

Rabbit No / Sex	Region of eye		One hour	24 h	48 h	72 h
3239	Cornea		0	0[1]	0	0
Female	Iris		0	0	0	0
	Conjunctiva	Redness	1	1	0	0
		Chemosis	1	0	0	0
		Discharge	1	1	0	0
3240	Cornea		0	0[1]	0	0
Male	Iris		0	0	0	0
	Conjunc-tiva	Redness	1	0	0	0
		Chemosis	0	0	0	0
		Discharge	1	0	0	0
3241	Cornea		0	0[1]	0	0
Female	Iris		0	0	0	0
	Conjunctiva	Redness	1	0	0	0
		Chemosis	0	0	0	0
		Discharge	1	1	0	0

1: 2% fluorescein sodium used to verify the absence of corneal opacity

All scores at each reading time (24, 48 and 72 hours) and for an effect are used for calculating the respective mean values. For each rabbit, the mean scores over 24, 48 and 72 hours were:

Chemosis	:	0.00	0.00	0.00
Redness of the conjunctive	:	0.33	0.00	0.00
Iris lesions	:	0.00	0.00	0.00
Corneal opacity	:	0.00	0.00	0.00

III. CONCLUSIONS

Based on this test, Surround® WP Crop Protectant is classified as non-irritating to the eye.

Current Conclusions

These GLP studies, conducted to internationally recognised guidelines, continue to be supportive of Surround® WP Crop Protectant with respect to eye irritation.

The results have been reinterpreted and based upon the outcome of the studies, and considering both the tiered evaluation described by ECHA (2017)[5] and lack of evidence from human exposure, Surround® WP Crop Protectant is classified as non-irritating to the eye (EC) 1272/2008.

CA 5.2.6 Skin sensitisation

Report:	KCA 5.2.6/01, [redacted], 2017
Title:	Assessment of sensitising properties on albino guinea pigs. Maximisation test according to Magnusson and Kligman.
Report No:	SMK-PH-17/0024 R1
Guidelines:	OECD Test Guideline No. 406; Method B.6 of Council Regulation No. 440/2008.
GLP:	Yes

Executive summary

The aim of the study was to evaluate the possible sensitising potential of aluminium silicate after intradermal and topical administration to guinea pigs. The induction phase (intradermal injection at 10% and topical application at 40%) was conducted using 10 guinea pigs and a 10-day rest phase. The challenge phase conducted under occlusive dressing for 24 hours, consisted of a single topical application of the test item diluted at 40% and 20% in distilled water. 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 after the challenge phase. 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 after the challenge phase. In conclusion, under the experimental conditions of this study, aluminium silicate does not have the potential to induce skin sensitisation.

[5] ECHA (2017). Guidance on the Application of the CLP Criteria. Version 5.0 – July 2017

I. MATERIALS AND METHODS

A. MATERIALS

1. **Test material:** Aluminium silicate (Calcined Kaolin)

   Description: White powder

   Batch No.: 61014E

   Purity: 99%

B. STUDY DESIGN AND METHODS

1. **Test animals:** **A**lbino guinea pigs (Dunkin-Hartley strain)

   Age: 3 to 4 weeks old

   Source: Envigo (Kreuzelweg 53, 5961 NM HORST - The Netherlands)

   Acclimation: Minimum 5 days

   Diet: Envigo 2040C, *ad libitum*

2. **Dose preparation:** The test item was used freshly prepared in physiological saline for the intradermal injections and in distilled water for the topical applications.

3. **Animal housing:** The animals were housed in groups of 3 (maximum) in polycarbonate containers, the flooring of which was covered with dust-free cuttings[6] and the top fitted with a stainless-steel lid with a feeding device and drinking bottle of 500 mL. Drinking water (tap water from public distribution system) was supplied *ad libitum.*

4. **Environmental conditions:**

   Temperature: 19 to 25 °C
   Relative humidity: 30 to 70%
   Photoperiod: 12 hours light (07.00 to 19.00) and 12 hours dark

5. **Preparation of animals**

Before study, animals were identified individually by marking with picric acid and by means of a numbered ring on the edge of one ear. The animals were specifically shorn before each test item application:

[6] i.e. wood shavings

- inter-scapular zone for the induction phase

- dorso-lumbar zone for the challenge phase

At least 3 hours before the first reading (challenge phase) they were shorn a second time in the dorso-lumbar zone. The animals were weighed at the beginning of the test, after the second induction and at the end of the test.

6. Preliminary studies:

Determination by intradermal injection of the Maximal Non-Necrotising Concentration (MNNC)

This was conducted for the purpose of defining an MNNC of the test item which, on intradermal injection during the induction phase, does not risk causing too great a lesion (non-necrotising concentration). Two animals received a volume of 0.1 mL of the test item, on both sides of the spine, at 4 concentrations: 20%, 10%, 5% and 2% (diluted in physiological saline). A macroscopic evaluation of the cutaneous reactions was conducted 24 hours after the injections to determine the MNNC.

Determination by topical application of the Pre-Maximal Non-Irritant Concentration (Pre-MNIC)

This allowed the evaluation of the irritancy potential of the test item and defined whether an application of sodium lauryl sulfate would be needed during the topical induction phase. The test item was applied on the dorso-lumbar zone of two guinea pigs (shorn beforehand), with occlusive dressing for 24 hours, at 4 different concentrations: 40%, 30%, 20% and 10% (diluted in distilled water). After the removal of the occlusive dressing, the treated areas were rinsed with distilled water. A macroscopic evaluation of the cutaneous reactions was conducted 24 hours after removal of the dressing to determine the pre-MNIC.

Determination by topical application of the Maximal Non-Irritant Concentration (MNIC)

This was carried out to determine the MNIC of the test item to ensure there was no risk of an irritant effect during the challenge phase. Three guinea pigs were treated according to the same treatment as animals from GROUP 1 (control) for the induction phase (i.e. physiological saline and distilled water). During the challenge phase, the animals were treated with the test item placed onto the selected treatment sites and covered with an occlusive dressing for a period of 24 hours at 4 different concentrations: 40%, 30%, 20% and 10% (diluted in distilled water). After removal of the occlusive dressing, the treated areas were rinsed with distilled water. A macroscopic evaluation of the cutaneous reactions was conducted 24 and 48 hours after removal of the occlusive dressing to determine the MNIC.

7. Main study:

GROUP 1 (negative control): 5 female guinea pigs

GROUP 2 (treated): 10 female guinea pigs

Induction phase

1st Intradermal Induction:

Day 0

After shearing the scapular zone, three pairs of intradermal (ID) 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:

GROUP 1 (control):

- 2 ID: Freund's Complete Adjuvant diluted at 50 % in physiological saline
- 2 ID: physiological saline
- 2 ID: a mixture with equal volumes of Freund's Complete Adjuvant at 50% and physiological saline

GROUP 2 (Treated):

- 2 ID: Freund's Complete Adjuvant diluted at 50 % in physiological saline
- 2 ID: test item at 10% in physiological saline
- 2 ID: a test mixture in equal volumes Freund's Complete Adjuvant at 50% and the test item at 20% in physiological saline

2nd Topical Induction:

Day 7

The scapular zone of all the animals in each group (shorn beforehand), was brushed with a solution of sodium lauryl sulfate at 10% in thick Vaseline®, to create local irritation.

Day 8

A topical application under occlusive dressing (25mm x 25mm non-woven swab of 4-layer gauze) in contact with the skin by means of 50 mm wide hypoallergenic adhesive tape for 48 hours was performed on the injection sites of each animal as follows:

GROUP 1 (control): 0.5 mL of distilled water

GROUP 2 (treated): 0.5 mL of the test item at 40% in distilled water

Day 10

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

Rest phase

The animals of both groups were left for 10 days.

Challenge phase

Day 21

The experimental procedure of this phase was identical for both groups GROUP 1 (Control) and GROUP 2 (Treated). To the previously shorn dorso-lumbar zones, a 24-hour application, under occlusive dressing, was performed as follows:

- 1 sample cup containing the test item diluted at 40% (MNIC)
- 1 sample cup containing the test item diluted at 20% in distilled water (½ MNIC).

Day 22

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

Day 23

1st reading time – 24 hours after the patch removal.

Day 24

2nd reading time – 48 hours after the patch removal.

7. Interpretation of results:

According to the scoring, the test item would be regarded as a skin sensitiser if 30% or more of the test animals show a sensitisation response. With regards to the current EU-based classification systems, the following classification and labelling requirements would be necessary for the test if it were concluded to be a skin sensitiser:

- In accordance with the Regulation (EC) No 1272/2008, the test item would be classified in Category 1. The signal word "Warning" and hazard statement H317 "May cause an allergic skin reaction" would be required.
- In accordance with the Regulation (EC) No. 286/2011, the test item would be classified in sub-category 1A or 1B as described below:

	Criteria
Sub-category 1A	≥ 30 % responding at ≤ 0.1 % intradermal induction dose or ≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose
Sub-category 1B	≥ 30 % to < 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose or ≥ 30 % responding at > 1 % intradermal induction dose

II. RESULTS AND DISCUSSION

Preliminary studies

MNNC determination

24 hours after the injections, slight necrosis to moderate erythema was observed at the tested concentration of 20%. Moderate to discrete erythema was noted at the tested concentrations of 10%, 5% and 2% in all animals. Consequently, the first induction of Group 2 was performed (by intradermal injection) at the maximal non-necrotising concentration of 10% (see below).

Table 5.2.6-1 Macroscopic evaluation of cutaneous reactions

Injection	Animal No.	CONCENTRATIONS			
		20%#	10%	5%	2%
Intradermal injection	C8869	SINe	2	1	1
	C8870	2	2	1	1

#: Maximum concentration administrable by intradermal route

SINe: Slight necrosis

Grading scale
0....No visible change
1....Discrete or patchy erythema
2....Moderate and confluent erythema
3....Intense erythema and swelling

Maximal Non-Necrotising Concentration	10%

Pre MNIC determination

24 hours after the removal of the occlusive dressings, no cutaneous reactions were noted irrespective of the concentration tested. In view of these results, the concentration selected was 40% for the 2nd induction of Group 2 and the MNIC determination began at a concentration of 40%.

MNIC determination

24 and 48 hours after removal of the occlusive dressings, no cutaneous reactions were noted irrespective of the concentration tested. In view of these results, the concentrations selected were 40% (MNIC) and 20% (½ MNIC).

Main study

Induction phase Group 1

No cutaneous reaction was noted during the induction phase.

Induction phase Group 2

24 hours after the first induction, moderate erythema was noted in all animals (10/10). Discrete erythema associated with dryness of the skin was noted in all animals (10/10) 24 hours after the second induction.

Challenge phase Groups 1 & 2

The overall results of the challenge phase with the test item (readings at 24 and 48 hours) are presented below. 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 after the challenge phase. 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 after the challenge phase.

Table 5.2.6-2

Macroscopic evaluation of cutaneous reactions (readings at 24 and 48 hours)

Groups	Timepoint	Concentration	INCIDENCE				% of positive responses ≥1	% of animals sensitized #
			0	1	2	3		
Group 1 (Control)	24 h	40%	5	0	0	0	0%	N/A
	48 h	40%	5	0	0	0	0%	N/A
	24 h	20%	5	0	0	0	0%	N/A
	48 h	20%	5	0	0	0	0%	N/A
Group 2 (Treated)	24 h	40%	10	0	0	0	0%	0%
	48 h	40%	10	0	0	0	0%	0%
	24 h	20%	10	0	0	0	0%	0%
	48 h	20%	10	0	0	0	0%	0%

N/A: Not applicable

Grading scale
0.....No visible change
1.....Discrete or patchy erythema
2.....Moderate and confluent erythema
3.....Intense erythema and swelling

#A comparison of the intensities and persistence of reactions at the test item challenge sites in the test and control animals permits identification of sensitization reactions. If the test item at the maximum non-irritant concentration produces reactions in test group animals at the 24 or 48-hour readings, these reactions are attributed to skin sensitization. This pre-supposes that no similar reactions were observed in the test item challenge sites of any of the control group animals. If irritation is observed in the control group animals, only reactions in the test group animals that exceed the most severe reaction seen in the control group animals are attributed to skin sensitization. The number of test group animals showing skin reactions greater than the most severe reaction observed in the control group animals is expressed as a percentage of test group animals.

Body-weight measurements

No abnormality in bodyweight gain was recorded in either of the groups.

Mortality

There was no mortality during the study.

III. CONCLUSION

Under the experimental conditions of this study, aluminium silicate does not have the potential to induce skin sensitisation. No classification is warranted according to (EC) 1272/2008.

CA 5.2.7 Summary of Acute Toxicity

Parameter	Species	Result	Reference
Acute Oral LD_{50}	Rat	> 5000 mg/kg	[redacted] (1997a)
Acute Oral LD_{50}	Rat	> 5000 mg/kg	[redacted] (1997b)
Acute Dermal LD_{50}	Rat	> 5000 mg/kg	[redacted] (1997)
Acute Inhalation LC_{50}	Rat	> 2.07 mg/l	[redacted] (1997a)
Acute Inhalation LC_{50}	Rat	> 2.18 mg/l	[redacted] (1997b)
Acute Skin Irritation	Rabbit	non-irritating	[redacted] (1997)
Acute Eye Irritation	Rabbit	non-irritating	[redacted] (1997)
Acute Eye Irritation	Rabbit	non-irritating	[redacted] (2000)
Skin sensitisation	Guinea pig	non-sensitising	[redacted] (2017)

Aluminium silicate (kaolin) is nontoxic via the oral, dermal or inhalation route to rats. Furthermore, it is not irritating to either eyes or skin nor is it a skin sensitiser. Based on the evidence presented aluminium silicate (kaolin) does not warrant classification.

CA 5.2.8 Phototoxicity

As aluminium silicate is an inorganic substance of infinite covalent structure, the molecular structure makes it impossible to absorb light energy. Therefore, the performance of a phototoxicity study is scientifically unjustified. Consequently, no study is submitted and the Notifier requests a waiver for the data requirement.

CA 5.3 Short-Term Toxicity

No short-term toxicity studies on aluminium silicate (kaolin) are available. Considering that aluminium silicate (kaolin) has an excellent safety record for continuous use as a food additive, pharmaceutical ingredient, personal hygiene component and in many industrial applications; short-term toxicity endpoints are waived.

CA 5.4 Genotoxicity Testing

No genotoxicity studies on aluminium silicate (kaolin) are available. Considering that aluminium silicate (kaolin) has an excellent safety record for continuous use as a food additive, pharmaceutical ingredient, personal hygiene component and in many industrial applications~~; genotoxicity toxicity endpoints are waived~~.

One genotoxicity study on Asian sand dust particles that used Kaolin as a reference substance was located and is presented below.

Report:	KCA 5.4/01, Yanagisawa, R., Takano, H, Ichinose T., Mizushima, K., Nishikawa, M., Mori, I., Inoue, K-I., Sadakane, K., Yoshikawa, T., 2007.
Title:	Gene Expression Analysis of Murine Lungs Following Pulmonary Exposure to Asian Sand Dust Particles
Report No:	Exp Biol Med 232:1109–1118, 2007
Guidelines:	No
GLP:	No

Executive summary

The effects of Asian Sand Dust Particles (ASDPs) on gene expression in the murine lung using microarray analysis were studied and elucidated the components responsible for lung inflammation. Male ICR mice were intratracheally administrated ASDPs, heat-treated ASDPs (ASDP-F, lipopolysaccharide [LPS], or b-glucan free), or kaolin particles. Microarray analysis was conducted on the murine lungs, the results of which were confirmed by quantitative reverse transcription–polymerase chain reaction (RT-PCR). Protein expression was assessed as were histologic changes. Exposure to ASDP, ASDP-F, or kaolin upregulated (>2-fold) 112, 36, or 9 genes, respectively, compared with vehicle exposure. In particular, ASDP exposure markedly enhanced inflammatory response–related genes, including chemokine (C-X-C motif) ligand 1/keratinocyte-derived chemokine, chemokine (C-X-C motif) ligand 2/macrophage inflammatory protein-2, chemokine (C-C motif) ligand 3/macrophage inflammatory protein-1a, and chemokine (C-X-C motif) ligand 10/interferon-gamma–inducible protein-10 (>6-fold). The results were correlated with those of the quantitative RT-PCR and the protein expression analyses in overall trend. In contrast, exposure to ASDP-F attenuated the enhanced expression of these proinflammatory molecules. Kaolin exposure increased the expression of genes and proteins for the chemokines. In histopathologic changes, exposure to ASDP prominently enhanced pulmonary neutrophilic inflammation, followed by kaolin and ASDP-F exposure in that order. Exposure to ASDP causes pulmonary inflammation via the expression of proinflammatory molecules, which can be attributed to LPS and b-glucan absorbed in ASDPs.

I MATERIALS AND METHODS

A. MATERIALS

1. Test Materials:

ASDPs were collected from desert surface soils at Shapotou Desert. Kaolin (ASP product no. 400; Engelhard Corp., Iselin, NJ), a white crystal used as an adhesive, was selected because its diameter is similar to that of ASDP. ASDPs and kaolin were sieved before use. The mean distribution peak of ASDP or kaolin diameter was observed at 5.5 or 4.8 µm, respectively. In some cases, LPS and b-glucan contained in ASDPs were inactivated by heat sterilization at 350°C for 30 mins before use (ASDP-F).

2. Test animals –

Species:	Mice
Strain:	ICR
Age:	Males five weeks old
Weight:	28-32 g

Source:	CLEA Japan Inc. (Kanagawa, Japan)
Acclimation:	Not specified
Diet:	CE-2 (CLEA Japan)
Water:	*ad libitum*
Housing:	Not specified

Environmental conditions –

Temperature:	22 - 26ºC
Humidity:	40% - 69%
Air changes:	Not specified
Photoperiod:	12-hour light/dark cycle

B. STUDY DESIGN AND METHODS

1. In life dates: during 2006

2. Animal assignment and treatment

The animals were randomly allocated to four experimental groups. The vehicle group received phosphate-buffered saline (PBS) at pH 7.4 (Invitrogen Co., Carlsbad, CA). The ASDP-F group, the ASDP group, and the kaolin group received 250 µg ASDP-F, ASDP, or kaolin in the same vehicle, respectively. In each group, mice were anesthetized with 4% halothane (Takeda Chemical Industries Ltd., Osaka, Japan), and then intratracheally inoculated 100-µl aliquots via a polyethylene tube.

3. Microarray Analysis.

Total RNA from lungs was extracted with ISOGEN (Nippon Gene, Tokyo, Japan) 4 hrs after the intratracheal inoculation and then was purified using RNeasy mini kit (Qiagen Ltd., Clifton, Australia) according to the manufacturer's instructions. Total RNA was converted to cDNA with Superscript choice for cDNA synthesis (Invitrogen) and was subsequently converted to biotinylated cRNA with an Enzo High-Yield RNA Transcript labelling kit (Enzo Diagnostics, Farmingdale, NY). Microarray hybridization was performed by Mouse Expression Array 430A (Affymetrix, Santa Clara, CA). After hybridization, the gene chips were automatically washed and stained with streptavidin-phycocrythrin using a fluidics system. The chips were scanned with a Hewlett Packard GeneArray Scanner (Loveland, CO). From data image files, gene transcript levels were determined using algorithms in the Microarray Analysis Suite Version 5 software (Affymetrix). The microarray analysis was performed with four mice combined in each group, which was confirmed by two separate series of experiments using a total of eight microarrays. Differences between vehicle- and particle-treated mice and those between ASDP-F– and ASDP-treated mice also were determined using GeneSpring software (Silicon Genetics, Redwood City, CA). Genes that were significantly upregulated by more than 2-fold or down-regulated by more than 0.5-fold in two separate series of experiments under the same conditions were averaged. The genes were categorized by the biologic process using NetAffyx Analysis.

4. Quantitative RT-PCR Analysis.

Total RNA was treated with DNase I (TaKaRa BIO Inc., Osaka, Japan) and then was purified with phenol/chloroform/isoamyl alcohol. This RNA was reverse transcribed to cDNA using MuLV reverse transcriptase according to the manufacturer's instructions (Perkin-Elmer Corp., Foster City, CA). The quantitation of mRNA expression was carried out using the ABI Prism 7000 Sequence Detection System (Perkin-Elmer). The quantitation of gene expression was derived using the standard curve method according to the manufacturer's protocol. The relative intensity was normalized to an endogenous control gene (18S rRNA). TaqMan probes and pairs for chemokine (C-X-C motif) ligand 1/keratinocyte-derived chemokine (CXCL1/KC), chemokine (C-X-C motif) ligand 2/macrophage inflammatory protein-2 (CXCL2/MIP-2), chemokine (C-C motif) ligand 3/macrophage inflammatory protein-1alpha (CCL3/MIP-1a), chemokine (C-X-C mot if) ligand 10/interferon-gamma–inducible protein-10 (CXCL10/IP-10), and 18S rRNA were designed and purchased from Perkin-Elmer, which did not disclose these sequences.

5. Enzyme-Linked Immunoabsorbent Assay (ELISA).

Murine lungs were removed 24 hrs after the intra-tracheal instillation. They were homogenized and centrifuged, and then the supernatants were recovered. ELISAs for CXCL1/KC, CXCL2/MIP-2, CCL3/MIP-1a, and CXCL10/IP-10 (all from R&D Systems, Minneapolis, MN) in the lung tissue supernatants were conducted according to the manufacturer's instruction. The detection limits of CXCL1/KC, CXCL2/MIP-2, CCL3/MIP-1a, and CXCL10/IP-10 were: 2 pg/ml, 1.5 pg/ml, 1.5 pg/ml, and 2.2 pg/ml, respectively.

6. Histologic Evaluation.

Murine lungs were removed 24 hrs after the intratracheal instillation. The lungs were fixed by intratracheal instillation of 10% neutral phosphate-buffered formalin (pH 7.2) at a pressure of 20 cm H_2O. After separation of the lobe, 2-mm–thick blocks were taken for paraffin embedding. Sections 3 µm thick were stained with haematoxylin-eosin. Histologic analyses were performed using a microscope (AX80; Olympus, Tokyo, Japan).

II. RESULTS AND DISCUSSIONS

A. FINDINGS

The findings from this study are expressed in the tables (taken directly from the paper) below and focus mostly on kaolin.

The content of elements in the particles:

Components	Element fraction (%) ASDPs	Kaolin
SiO_2	60.0	45.4
Al_2O_3	11.1	38.8
Fe_2O_3	4.1	0.3
Na_2O	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

The content of LPS and b-glucan in the particles:

	LPS (EU/mg particles)	β-glucan (pg/mg particles)
ASDP-F	3.70×10^{-4}	0.14
ASDP	3.66	15.20
Kaolin	3.26×10^{-4}	0.13

Number of upregulated or downregulated genes:

Group	>2.0	<0.5
ASDP-F versus vehicle	36	0
ASDP versus vehicle	112	3
Kaolin versus vehicle	9	0
ASDP versus ASDP-F	82	1

Upregulated genes – Average ratio ± SD:

Kaolin versus vehicle (3 genes)	**Chemokine (C-X-C motif) ligand 1**	13.85	8.27
	Histocompatibility 2, D region locus 1	6.60	5.60
	Chemokine (C-X-C motif) ligand 2	6.46	2.17

Upregulated genes – Accession number and biologic process description:

Kaolin versus vehicle (3 genes)	NM_008176	Inflammatory response
	M83244	Immune response
	NM_009140	Inflammatory response

Protein expression analysis in the lungs:

	Pg/total lung supernatants			
Group	CCL3/MIP-1α	CXCLI/KC	CXCL2/MIP-2	CXCL10/IP-10
Vehicle	0.0	0.0	0.2 ± 0.2	47.1 ± 3.25
ASDP-F	5.92 ± 2.62	11.9 ± 3.89	4.94 ± 1.54	40.1 ± 1.31
ASDP	180 ± 22.7**,##	379 ± 34.6**,##	285 ± 49.9**,##	684 ± 161**,#
Kaolin	131 ± 17.7**	355 ± 59.0**	125 ± 30.0*	128 ± 28.4**

[a] Four groups of mice were intratracheally instillated with vehicle, ASDP-F, ASDP, or kaolin. Lungs were removed 24 hrs after instillation. Protein levels of inflammatory molecules in the lung tissue supernatants were analyzed using ELISA. Data are the means ± SEM of 8 animals per group.
*$P < 0.05$ versus vehicle group; **$P < 0.01$ versus vehicle group; #$P < 0.05$ versus ASDP-F group; ##$P < 0.01$ versus ASDP-F group.

III. CONCLUSIONS

Intratracheal administration of ASDP elevated (>2-fold) the expression of 112 genes compared with vehicle administration. Exposure to ASDP-F upregulated 36 genes, which was accompanied by neither the gene expression nor the protein expression related inflammatory response such as chemokines.

In histopathological analyses, exposure to ASDP enhanced neutrophil inflammation in the murine lungs, which was followed by kaolin and ASDP-F exposure in that order.

Kaolin administration upregulated the expression of several proinflammatory genes (only nine genes) (CXCL1/KC and CXCL2/MIP-2) and proteins (CXCL1/KC, CXCL2/MIP-2, CCL3/MIP-1a, and CXCL10/IP-10), in spite of the absence of LPS or b-glucan. In addition, kaolin exposure also induced neutrophilic lung inflammation. These results suggest the importance of these chemokines in the lung inflammation, whereas the gene expression of the chemokines 4 hrs after the intratracheal instillation was only slightly different from their protein expression 24 hrs after the instillation.

CA 5.5 Long-Term Toxicity and Carcinogenicity

No long term-carcinogenicity studies (mice or rat) on aluminium silicate (kaolin) are available. Considering that aluminium silicate (kaolin) has an excellent safety record for continuous use as a food additive, pharmaceutical ingredient, personal hygiene component and in many industrial applications; long term-carcinogenicity toxicity endpoints are waived.
However, two publications were available for review.

Report:	KCA 5.5/01, Schepers G W H, 1971
Title:	Lung tumors of primates and rodents Including a12 months study, tracheal injections, guinea pigs
Report No:	Industrial Medicine, Vol. 40 (1), pp32-37.
Guidelines:	Not applicable.
GLP:	Not stated; published article.

Materials and methods

This paper presented several series of experimental animals exposed by tracheal injection and inhalation methods to a variety of chemical substances. Kaolin was administered by tracheal injection in guinea pigs. Guinea pigs (2862 animals) received 130 substances (or combinations of substances) by the intratracheal route.

Batch No and purity of aluminium silicate (kaolin): Not reported
Animals tested: Guinea pigs; strain and origin not reported

Findings

The results obtained with the guinea pigs are shown below:

Table 5.5-1: Lungs tumors experimentally induced in guinea pigs

Treated animals			Controls		
Animal No	Tumors		Animal No	Tumors	
	No	%		No	%
4294	11	0.26	1878	0	0

11 tumors were found, limited to two substances. The controls for these groups, displayed no tumors.

Table 5.5-2: Pulmonary lesions experimentally induced in guinea pigs Tracheal route – 12 months

Substance	Lesions observed		
	O	E	N
Kaolin	+	-	-

O: all other lesions: not reported in this paper; E: Epithelialization; N: Neoplasia; -: No lesion; + : Slight reaction; ++: Moderate reaction

Conclusions

Intratracheal injection of a suspension or solution of any chemical substance was not necessarily pathogenic. It may be argued that the intratracheal route creates highly artificial local conditions that could induce pulmonary lesions. To a degree, the intratracheal method may exacerbate the biological effects of some 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. In this study aluminium silicate (kaolin) administered during 12 months via the intratracheal route to the guinea pig did not induce any epithelialization or neoplasia lesion.

Report:	KCA 5.5/02, Wagner J C, Griffiths D M, Munday D E, 1987
Title:	Experimental studies with palygorskite dusts
Report No:	Br. J. Ind. Med. 44:749-763.
Guidelines:	Not applicable.

GLP:	Not stated; published article.

Materials and methods

Aluminium silicate (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 mine, Lebrija and Leicester.

Test animals:
Species: Rat
Strain: Fischer, SFP, F344

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. At 3, 6 and 12 months, four animals were killed and subject 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.

Findings

At microscopic examination, 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 Leicester Attapulgite, proliferative lesions observed included two mesotheliomas, one peritoneal mesothelioma, one malignant alveolar neoplasm, two benign alveolar neoplasms, and eight broncho-alveolar hyperplasias. Twenty-seven rats had no proliferative lesions. Rats exposed to the negative-control Kaolin had two broncho-alveolar tumors. Rats in the positive-control Crocidolite group had one adenocarcinoma and three bronchoalveolar tumors. The mean fibrosis grades of each treatment group are presented in Table 5.5-3:

Table 5.5-3: Toxicity of inhaled Attapulgite dust vs Kaolin
Rats – Inhalation route – 24 months

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

The classification of proliferative lesions and neoplasms corresponding to the mean fibrosis grades are as follows:

(1) bronchoalveolar hyperplasia - no malignant proliferation of the epithelia,
(2) benign alveolar neoplasm,
(3) malignant alveolar neoplasm,
(4) adenocarcinoma,
(5) squamous carcinoma,
(6) adenosquamous carcinoma,
(7) mesothelioma.

The Lebrija Attapulgite dust extracted from the animal lungs did not have short fibres and the presence of granular material found to be Mica on analysis. The Leicester Attapulgite dust also had the presence of long fibres. Kaolin is a non-fibrous dust. Crocidolite is a fibrous dust, but lengths were not published in this study.

Conclusions

Aluminium silicate (kaolin), administered during 12 months to the rat in an inhalation chamber did not induce any malignant lesion.

CA 5.6 Reproductive Toxicity

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.

The only study submitted concerning the reproductive toxicity of Kaolin is as follows.

Report:	KCA 5.6/01, Patterson E C, Staszak D J, 1977
Title:	Effects of geophagia (kaolin ingestion) on the maternal blood and embryonic development in the pregnant rat
Report No:	J. Nut. 107:2020-2025
Guidelines:	Not applicable.
GLP:	Not stated; published article.

Materials and methods

The aim of this study was to determine the effect of kaolin (clay) ingestion on the maternal blood and embryonic development of the pregnant rat.

Test Material: Aluminium silicate (kaolin) used throughout the experiment and was obtained from the research department of one of the kaolin mines located in Twiggs County, Georgia. The clay was described as air-floated which had not been treated in any manner or

undergone any chemical alteration. The chemical analysis of this clay gave the following results:

Portion	%
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 on ignition	13.48

Test animals

Species:	Rat
Strain:	Sprague-Dawley, ARS
Age:	Adults, male and female
Weight at dosing:	201 to 225 g for the females
Source:	Mogul Corp., Madison, Wisconsin
Acclimation:	Not stated

Diet:	Laboratory Chow, Ralston Purina Company, St. Louis, Missouri
Water:	Tap water in glass bottles equipped with stainless steel spouts
Housing:	The rats were individually housed in single, standard rat cages during the gestation period in a certified animal room

Environmental conditions:

Temperature: 23 ± 2ºC

No monitoring or regulation of humidity or light was reported.

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, haematocrit, 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 haematocrit, 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.

Conclusions

No teratogenic effects were observed in this investigation.

CA 5.7 Neurotoxicity Studies

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'[7] 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

[7] The presentation titled 'Activities of EFSA in the area of aluminium' was delivered by the EFSA representative, Prof. Dr George E.N. Kass (A member of EFSA's 'Food Ingredients and Packaging Unit'), on 26th November 2014 as part of the '15th BfR Consumer Protection Forum' titled "Aluminium in Everyday Life: A Health Risk? Intake of Aluminium from Food, Cosmetics and other Consumer Products". The presentation provides and overview and background covering the decisions leading to Regulation (EU) No. 380/2012. Slide 35 is the most pertinent to aluminium silicate.

The EFSA presentation is available to view directly from the BVL website:
http://www.bfr.bund.de/cm/343/activities-of-efsa-in-the-area-of-aluminium.pdf [accessed December 2017]

Details of the '15th BfR Consumer Protection Forum' are also available from the BVL website:
http://www.bfr.bund.de/en/event/15th_bfr_consumer_protection_forum__aluminium_in_everyday_life__a_health_risk__intake_of_aluminium_from_food__cosmetics_and_other_consumer_products_-191395.html [accessed December 2017]

"*Aluminium silicate could be considered a candidate for the inclusion in Annex IV of Commission Regulation (EC) No 396/2005*".

CA 5.8 Other Toxicological Studies

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

CA 5.8.1 Endocrine disrupting properties

The evidence from available studies does not suggest that aluminium silicate could be considered as an endocrine disrupting chemical, i.e. it does not cause adverse developmental, reproductive, neurological, and/or immune effects in both humans and other animals.

CA 5.9 Medical Data

CA 5.9.1 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 because of exposure to kaolin in its solid, liquid or respirable forms. Some cases of pneumoconiosis were reported in the late 1970s and 1980s, which were the result of exposure far more than current ACGIH TLVs (American Conference of Governmental Industrial Hygienists; Threshold Limit Values), dating in some cases back to the 1930s. With good dust control practices over the last 25 years no new cases of kaolin caused pneumoconiosis were found. Supportive evidence can also be drawn from studies of English china clay workers[8].

CA 5.9.2 Direct observations

Not applicable; aluminium silicate (kaolin) is not acutely toxic. No cases of poisoning incidents with kaolin have been reported.

CA 5.9.3 Epidemiological studies

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.

[8] 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

CA 5.9.4 Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests

Not applicable; aluminium silicate (kaolin) is not acutely toxic. No cases of poisoning incidents with aluminium silicate (kaolin) have been reported.

CA 5.9.5 Proposed treatment: first aid measures, antidotes, medical treatment

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.

CA 5.9.6 Expected effects of poisoning

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.

CA 5.10 Summary of Mammalian Toxicity

Aluminium silicate (kaolin) is not absorbed or metabolised in mammals.

Aluminium silicate (kaolin) is not acutely toxic by either the oral or dermal route and no signs of systemic toxicity or intoxication were observed at the maximum tested dose of 5000 mg/kg bw. It is therefore not classified.

No signs of toxicity were seen at the highest attainable concentration in the inhalation studies. Neither systemic toxicity nor intoxication was observed.

Aluminium silicate (kaolin) is not irritant to skin or eyes. Transient irritation to eyes was noted during the eye irritation studies, however irritation is fully reversible. The use of eye safety equipment is required when handling kaolin.

Aluminium silicate (kaolin) is not a skin sensitiser.

No sub-chronic, chronic, genotoxicity, carcinogenicity and reproduction toxicity studies were performed as kaolin is approved as a food additive and pharmaceutical ingredient and as such has been generally regarded as safe.

Direct observations in humans indicate that in the case of long-term exposure, kaolin may be an irritant to the lung. This risk appears to be limited to workers routinely exposed to fine kaolin dust and is not expected in end-users of Surround® WP Crop Protectant or members of the general public.

It is concluded that aluminium silicate (kaolin) can be considered as non-toxic by the oral, dermal and inhalation routes. It is not irritating to the eye or skin and is not a sensitizer.