

KAOLIN

SYNONYMS

AA Kaolin,
 ASP (mineral), ASP Ultrafine
 Acidic white clays
 Airflo V 8
 Alfaplate, Alphacoat, Alphagloss
 Altowhite, Altowhites
 Aluminium silicate hydroxide
 Amazon 88, Amazon 90, Amazon Kaolin 855D
 Apsilex
 Arcilla Blanca
 Argiflex
 Argilla, Argilla alba
 Argirec B 22, Argirec KN 15
 Astra-Glaze
 BOL-Blanc
 Bentone
 Bilt Plate 156
 Bolus alba
 Burgess 10
 CB 1 (clay), CB 2 (clay), China clay, Clay 347,
 Comalco, Comalco Kaolin
 Emathlite
 Fitrol, Fitrol desiccate 25
 Glomax
 Hydrated aluminium silicate
 Hydrite
 Kaopaous
 Kaophilis-2
 Langford
 Parclay
 Porcelain clay
 Snow-tex
 Vanclay
 White bole
 Beta Coay

CHEMICAL STRUCTURE

Undefined mixture of components

CHEMICAL FORMULA



IDENTIFIER DETAILS

CAS Number : 1332-58-7
CoE Number : -
FEMA : -
EINECS Number : 310-194-1
E Number : E559

SPECIFICATIONS

Melting Point: Ill defined

Boiling point: Ill defined

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
-	-	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
-	-	-	-

FDA Status:[CFR21]

Section Number	Comments
178.3297	Indirect food additives: adjuvants, production aids, and sanitizers
186.1256	Indirect food substances affirmed as generally recognised as safe

HUMAN EXPOSURE

Natural Occurrence: kaolin is a clay that contains 10-95% of the mineral kaolinite and is formed by rock weathering. In addition to kaolinite, kaolin usually contains quartz and mica, and also less frequently, feldspar, illite, montmorillonite, ilmenite, anastase, haematite, bauxite, zircon, rutile, kyanite, silliminate, graphite, attapulgitite, and halloysite. Kaolin is a natural component of soil and found in air [HSDB, 2008]

Reported Uses: Kaolin is reportedly used in paper coating, cement, food additives, paper filling, pencil leads, bleaching extender in paint, adhesives, fertilizers, ceramic raw material, tanning leather, plaster, filler in rubber, pharmaceuticals, filter aids, filler in plastics, enamels, cosmetics, extender in ink pastes and glues crayons, petroleum, insecticides, detergents, fiberglass, medicines, roofing granules, foundry bond, sizing, linoleum, dessicants, textiles, polishing compounds [Murray, 2005].

TOXICITY DATA

Gosselin *et al.*, reported the minimum fatal dose level as 1; practically non-toxic and the probable oral lethal dose in humans above 15g/kg [Gosselin *et al.*, 1984].

***In Vivo* Toxicity Status**

Species	Test Type	Route	Reported Dosage
Rat	LD ₅₀	Oral	> 5000mg/kg
Rat	LD ₅₀	Dermal >	> 5000mg/kg

[HSDB, 2008]

Carcinogenicity and Mutagenicity

Cultured tracheas from hamsters with kaolin (diameter 3-5 um) and kaolin coated with 3-methylcholanthrene, were implanted in to the tracheas after 4 weeks into syngeneic hamsters, and monitored until moribund at 105-110 weeks. Animals treated with kaolin did not develop tumours, but a high incidence of pulmonary tumours, often fatal, was observed in animals treated with kaolin coated with 3-methylcholanthrene. Animals treated with 3-methylcholanthrene coated hematite or carbon particles also developed a similar spectrum of tumours (carcinomas, sarcomas, undifferentiated tumours) [HSDB, 2008].

Dermal Toxicity

No dermal irritation was reported in rabbits treated with 0.5 g kaolin for 4 hours. No toxicity or any other clinical abnormalities were observed throughout the study [USEPA/Office of pesticide Programs, 2000].

Reproductive and Developmental Toxicity

The intent of this study was to determine the effects of kaolin ingestion on the maternal blood and embryonic development of the pregnant rat. Thirty-six Sprague-dawley female rats were divided into three groups: control diet, 20% kaolin diet, and iron-supplemented 20% kaolin diet. The diets were fed 37 to 68 days, 69 to 95 days, and 96 to 117 days prior to fertilization, and the same diets were fed for the duration of the gestation period. The rats fed the kaolin diet exhibited significant reductions in hemoglobin, hematocrit, and red blood cell levels, thus indicating maternal anemia. There was also a significant reduction in the birth weight of the pups born to kaolin fed rats. The kaolin fed rats receiving an iron supplement maintained hematocrit, hemoglobin, red blood cell levels, and pup weight within the normal range [Patterson *et al.*, 1977].

Inhalation Toxicity

Many case reports and case series have suggested that exposure to kaolin causes pneumoconiosis. In several case however, it is not clear whether kaolinite and quartz or quartz alone is responsible for the resulting pneumoconiosis [IPS INCHEM, 2007].

Inhalation exposure to kaolin at an unspecified concentration 2 hours a day, every second day, twice weekly, or weekly for 6 months in groups of guinea-pigs produced mild alveolar proliferation up until 3 months. Thereafter, thickening of the alveolar walls, emphysema, and patchy bronchopneumonia with capillary congestion and massive eosinophil infiltration occurred. By 6 months, plaque formation and capillary bronchitis were observed [IPS INCHEM, 2007].

Guinea pigs and rats were exposed to airborne kaolin dust for 6 hours/day, 5 days/week for 1 year. Guinea pigs exposed at 23.4 mg/m³ showed slight pleural mottling. The lymph nodes contained large masses of dust cells. Rats exposed at 27.1 mg/m³ developed scattered dust foci; collagenous fibres were observed between the cells and the lymph nodes contained large masses of dust. Intratracheal injection of rats with kaolin dust was associated with similar reactions, but the coarser particles elicited a large number of foreign body giant cells [HSDB, 2008].

Other Relevant Studies

Intratracheal instillation of a single dose of commercial acid-washed kaolin containing 8% hydrated free silica and 12% mica was performed in 12 rats. Two animals were killed between days 3 and 6 and the rest kept up until 8 months. Grade 2 fibrosis was observed in rats after 8 months (grade 1=minimal reticulin fibrosis, grade 4 = maximal fibrosis) [Belt & King, 1945].

Single intratracheal instillation of kaolin, particle size < 5 µm was administered to 10-15 rats per group. Histological analysis of lungs was carried out after 4 months. Cellular lesions with minimal fibrosis were observed with some loose reticulin with either no collagen or a few collagen fibres in rats [Goldstein & Rendall, 1969].

Sahu *et al* described fibroblast reaction from 60 days post-exposure, prominent from day 120 and grade 2 fibrosis by day 210, in mice after intratracheal administration 5 mg of kaolin [Sahu *et al*, 1978].

Kaolinite 1 (K1) containing 2% muscovite; K2, 1% quartz and 9% muscovite; K3, < 1% quartz and anatase and 1% muscovite; and K4, 1% quartz and anatase and 2% muscovite were intratracheally administered once at 50 mg/kg of body weight to groups of 20 female wistar rats. Two samples of quartz was also investigated and the dose given at 5 mg/kg of body weight. Autopsy after 7 months, lung weight and histology were measured. All kaoline samples were fibrogenic. The fibrogenicity of kaolinites, as measured by the

increase in hydroxyproline content in relation to the amount of dust retained, was approximately 1/10 that of quartz, but the inflammatory reaction was considerably less [IPS INCHEM, 2007].

Intratracheal injection of 10 mg of kaolin containing 67% kaolinite and 23% quartz was administered to groups of 5 male rats. After 15, 30 and 60 days bronchopulmonary lavage was performed and LDH activity, and the protein and phospholipid content of the supernatant was measured. Kaolin did not induce significant LDH, protein, or phospholipid leakage to the supernatant fraction. Two quartz samples that were also examined however did increase the phospholipid content at 30 and 60 days [Adamis & Krass, 1991].

Female Sprague Dawley rats were administered 0.1 mL Kaolin (250 mg/mL) into cisterna magna. 1, 4 and 8 weeks later, brains were analyzed using antibodies against MHC class I (OX18), MHC class II (OX6), CD4 (OX38), CD8 (OX8), OX42, ED1, NF, GFAP, AChE and TH. Remarkably high numbers of T lymphocytes, and OX42- and ED1-positive macrophages were found aggregated in subarachnoid spaces, and in the third and fourth ventricles. Marked aggregations of ED1-positive reactive microglial cells were also found in paraventricular structures, medial septum, retrosplenic cortex and commissural structures. However, no such cells were found in hippocampus. ED1-positive areas were also positive for round cells with a rim of MHC I fluorescent cytoplasm as well as for OX42-positive cells and MHC II positive microglial cells. At week 1, in ventro-frontal areas of cortex, CD8-positive cells and MHC I positive astroglial fibers were detected. At week 1, MHC I positive ramified microglial cells were also recognized in almost the entire brain. These positive cells gradually decreased with time and finally remained rounded with a rim of fluorescent cytoplasm. In addition, ED1 positive partly ramified microglial cells could be recognized in corpus callosum, probably representing cells in transition between ramified and reactive microglia. CD8+ cells entered ventral brain structures, and were found in the horizontal diagonal band at week 4, and had disappeared at week 8. Finally in cortex, ED1 positive microglial cells could be identified only in the retrosplenic cortex, and there were also "dark shrunken neurons" in light microscopic stainings. However, there was only a moderate GFAP positive gliosis. The authors concluded kaolin-induced hydrocephalus leads to immune reactions in several defined areas such as cholinergic systems, corpus callosum, circumventricular organs, pontine cerebellar peduncles and the vestibular nucleus [Shinoda & Olson 1997]*

Behavioural data

Chronic hydrocephalus was studied in rats, 9 months after induction by kaolin injection into the cisterna magna, and in humans. In both circumstances, destruction of periventricular white matter structures was worst in those with the largest ventricles. Structures damaged include the corpus callosum, corticospinal tract, and fimbria/fornix projections from the hippocampus. Myelin turnover was increased. These changes were associated with deficits

of motor and cognitive function. The cerebral cortex was largely spared [Del Bigio *et al*, 2003].

***In Vitro* Toxicity Status**

Carcinogenicity and Mutagenicity

To examine genotoxic effects by C60, CB and kaolin, an *in vitro* micronuclei (MN) test was conducted with human lung cancer cell line, A549 cells. In addition, DNA damage and mutations were analyzed by *in vivo* assay systems using male C57BL/6J or gpt delta transgenic mice which were intratracheally instilled with single or multiple doses of 0.2 mg per animal of particles. *In vitro* genotoxic analysis revealed increased MN frequencies in A549 cells treated with C60, CB and kaolin in a dose-dependent manner. These three nano/microparticles also induced DNA damage in the lungs of C57BL/6J mice measured by comet assay. Moreover, single or multiple instillations of C60 and kaolin, increased either or both of gpt and Spi- mutant frequencies in the lungs of gpt delta transgenic mice. Mutation spectra analysis showed transversions were predominant, and more than 60% of the base substitutions occurred at G:C base pairs in the gpt genes. The G:C to C:G transversion was commonly increased by these particle instillations. It was concluded that manufactured nano/microparticles, CB, C60 and kaolin, were shown to be genotoxic in *in vitro* and *in vivo* assay systems [Totsuka *et al*, 2009]

Other Relevant Studies

The following table has been taken from IPCS INCHEM; Environmental Health Criteria (EHC) Monographs. Bentonite, kaolin, and selected clay minerals (EHC 231). Available from June 2007 (<http://www.inchem.org/documents/ehc/ehc/ehc231.htm>.)

System . species / gender	Dose (mg/ml)/ treatment	Findings
Peritoneal macrophages		
Rat (Sprague-Dawley CFY)	Two types of kaolin (90% kaolinite, 4% quartz; or 93% kaolinite, 4% quartz; diameter not given) incubated	Dye binding decreased the methylene blue adsorption to a third and the inhibition of T C reduction by one-

	with cells for 24 h either as such or after dry milling for 32 h	half to two-thirds.
Mouse (Swiss T.O.)	Kaolin (non-specified), 100 µg/ml, incubation for 18 h	Approximately 25% release of LDH and <i>beta</i> -glucuronidase release with native kaolin; one-half to two-thirds of the activity lost upon calcination.
Rat (Sprague-Dawley CFY), male	Six different kaolins, kaolinite content 51-95%, quartz content 5-20%; 1.0 mg/ml (<5 µm diameter, median 1-2 µm) incubated in cell suspension for 1 h	All 3 samples considered cytotoxic based on TTC reduction(except one (30%), which had 71% kaolinite and 22% quartz. All considered inert based on small LDH release, except the one with the highest quartz concentration (29%); the kaolinite concentration in this specimen was 67%.
Rat (Sprague-Dawley CFY), male	Four different kaolins (from Hungary, silica content 4, 5, 18, and 30%, <5 µm diameter, otherwise not specified) incubated in cell suspension for 24 h; similar experiment with a non-specified illite clay	Three out of four kaolins and illite considered cytotoxic based on TTC reduction; no relationship between quartz concentration and cytotoxicity. The clays studied did not induce release of LDH, but illite decreased intracellular LDH activity.
Mouse (T.O.), female	Culture of unstimulated macrophages with Cornwall kaolinite (not specified) for 18 h	Kaolinite induced LDH release from macrophages; this was prevented by polyvinylpyridine- <i>N</i> -oxide.
Mouse (T.O.), female	Cornwall kaolin (98% kaolinite, 2% mica), 98% <5 µm in diameter, incubated	Kaolinite induced a 70% LDH release to the medium; the release was partly prevented by

	with cells at 40 µg/ml for 18 h	treatment of kaolin with polyvinylpyridine- <i>N</i> -oxide and fully prevented by additional treatment with polyacrylic acid.
Rat (Wistar, SPF), both sexes	Kaolin (composition not specified, diameter 0.2-25 µm), 0.5 mg/10 ⁶ cells incubated for 2h	Of all cells with particles, 0.6% and 1.6% dead cells with particles at 1 and 2 h (lowest toxicity group of three).
Mouse	Fifteen respirable dust samples from kaolin drying and calcining plants in England (kaolinite content 84-96%, mica 3-6%, quartz 1 %, feldspar 0-7%), a sample of Cornish kaolin (K1, 98% kaolinite, no quartz or feldspar, 2% mica), and a sample of Georgia kaolin (K2, 99% kaolinite, no quartz, mica, or feldspar, and reference quartz DQ12, mica, gibbsite, and titanium dioxide as controls; incubation for 18 h with macrophages, LDH release measured	All dust samples were cytotoxic. The quartz content could not explain the cytotoxicity. The kaolinite samples showed a dose-dependent cytotoxicity, which could not be explained by their content of ancillary materials.
		Polyacrylic acid treatment of kaolin has only a small effect on its cytotoxicity, indicating that the positive charge at the edge of the mineral (blocked by acrylic acid) is not a major determinant of the toxicity.
Alveolar macrophages		
Rat (Wistar, SPF), both sexes	Kaolin (composition not specified, diameter 0.2-25 µm), 0.5 mg/10 ⁶ cells	Of all cells with particles, 3.7% and 4.2% dead cells with particles at 1 and 2 h

	incubated for 2h	(lowest toxicity group of three).
Rabbit (New Zealand)	Kaolinite (>99% pure), >99% respirable size, incubated with cells at 0.25-2.5 mg/ml	Kaolinite caused an inhibition of amino acid incorporation into protein in a dose-dependent manner, 65% inhibition at 1 mg/ml. Inhibition reversed by addition of serum.
Guinea-pig	Kaolin (non-specified), 100 µg/ml, incubation for 18 h	Approximately 30% release of LDH and <i>beta</i> -glucuronidase release with native kaolin; >90% of the activity lost upon calcination.
Rabbit (New Zealand)	Kaolin (unspecified) and illite clay (unspecified) (<5 µm diameter), 0.5 mg/ml incubated in cell suspension for 24 h	Kaolin induced a 15.3% release of LDH and a 7% release of alkaline phosphatase. Illite clay induced a 2% release of LDH and a 1.3% release of alkaline phosphatase. For quartz, the figures were 51 % and 16%.
Rat (Sprague-Dawley), male	Georgia kaolin (≥96% kaolinite, no quartz, >95% >5 µm in diameter), incubated with cells for 1 h at 0.1-1 mg/litre	Kaolin induced a dose-dependent release of LDH, <i>beta</i> -glucuronidase, and <i>beta</i> -N-acetylglucosaminidase of 60-80%. The effect was largely (9-15% release) abolished by lecithin.
Rat (strain not specified)	Kaolin, 1.0 mg/ml (<5 µm diameter, MMAD 2.1 µm) incubated in cell suspension for 2 h	Kaolin induced an 80% release of LDH and a 60% release of <i>beta</i> -glucuronidase and <i>beta</i> -N-acetylglucosaminidase, being most cytotoxic of all minerals studied, quartz

		included.
Leukocytes		
Human phagocytic cells from one donor	Well crystallized standard kaolinite KGa-1, no quartz, cristobalite, or mica, particle size 3.2 μm median volume diameter	Kaolinite at concentrations of approximately 1 mg/ml induced luminol-dependent chemiluminescence as an expression of generation of reactive oxygen species in both monocytes and neutrophils when opsonized and when not opsonized.
Erythrocytes		
Human washed erythrocytes	Erythrocytes incubated with Hungarian water-cleaned kaolin (composition not indicated; $<5\text{ }\mu\text{m}$ in diameter), as such or after heat treatment at 290-900 $^{\circ}\text{C}$ for 90 min	Kaolin was strongly haemolytic; heating for 90 min to 200 or 350 $^{\circ}\text{C}$ increased, but heating to 500 or 650 $^{\circ}\text{C}$ practically abolished, the haemolytic potency. Kaolin heated at 800 or 950 $^{\circ}\text{C}$ was at least as potent a haemolyser as non-treated kaolin.
Rat (strain not specified)	Kaolin (unspecified) and illite clay (unspecified) ($<5\text{ }\mu\text{m}$ in diameter) 1.0 mg/ml incubated in cell suspension for 1 h	Kaolin caused 98% haemolysis, illite 24% (quartz 48%).
Rabbit	Kaolin (non-specified), incubation for 50 min	Twenty per cent haemolysis caused by 1.3 mg kaolin in a total volume of 4 ml; 11.6 mg of calcined kaolin was needed for the same effect.
Human (citratd blood)	Six different kaolins, kaolinite content 51-95%, quartz content 5-20%; 1.0 mg/ml	Haemolysis 60-90% for all samples except one (30%), which had 71% kaolinite

	(<5 µm diameter) incubated in cell suspension for 1 h	and 22% quartz.
Human	One "bentonite," containing 50% illite, 25% montmorillonite, 25% quartz; two undefined illite clays, one kaolinite with dickite and nakrite as main components and quartz as a minor component, one kaolin with kaolinite as the main component, and two unspecified kaolins ground in a ball mill to diameter <5 µm, incubated in cell suspension for 1 h	Fifty per cent haemolysis caused by 1.5-4 mg/ml kaolinites (0.06-0.115 m ² /ml); and 1.0-4.0 mg/ml (0.039-0.12 m ² /ml) illites. Haemolytic activity roughly proportionate to surface area of mineral powder; haemolytic activity largely lost after heating to over 500 °C.
Neural cells		
Neuroblastoma (N1E-115) cells with differentiation induced by dimethylsulfoxide	Standard kaolinite KGa-1 0.1-1.0 mg/ml incubated in cell suspension	Within minutes, resting potential depolarized and ability to maintain action potentials in response to stimulation was lost; within 30 min, severe morphological deterioration of cells.
Neuroblastoma (N1E-115) cells and oligodendroglial (ROC-1) cells	South Carolina kaolinite (non-specified, mainly 1-2 µm diameter) incubated at 0.1 mg/ml in cell suspension for 24 h	No alteration of LDH activity in medium for either cell type; no decrease of the viability (assessed by trypan blue exclusion) of N1E-115 cells after 24 h.
Other cell types and <i>in vitro</i> systems		
Tracheal epithelial (cloned cell line from Syrian hamster,	Kaolinite 90% <2 µm in diameter at four concentrations, 0.003-0.1 mg/ml, incubated in cell	Cells phagocytized clay particles; dose-dependent damage to plasma membrane as evidenced

strain 87.20) in log growth phase in monolayer	suspension for 24 h	by loss of ^{51}Cr from cells; loss of ^{51}Cr after 24 h approximately 40% with 0.1 mg/ml, twice that of quartz.
Human umbilical vein endothelial cells	South Carolina kaolinite (non-specified, mainly 1-2 μm diameter) incubated at 0.1 mg/ml in cell suspension for 24 h	Kaolinite induced a statistically significant 50% increase in LDH activity in the medium and killed 90% of the cells in 24 h.
Macrophage-like cell line P338D ₁	Three kaolinites, 1 with "high crystallinity," 1 with "medium crystallinity," and 1 with "low crystallinity," diameter <5 μm , incubated at 80 $\mu\text{g}/\text{ml}$ for 48 h	Kaolinites caused a 78-91 % decrease in the viability of the cells and induced leakage of LDH and <i>beta</i> -N-acetylglucosaminidase. Adsorption of nitrous oxide on the minerals slightly decreased the effect on viability.
V79-4 Chinese hamster lung cell line	Non-specified kaolin incubated with the cells for 6-7 days	LD ₅₀ 20 mg/ml for kaolin, which was the most toxic of the 21 particulate and fibrous materials tested.
Macrophage-like cell line P338D ₁	Thirty respirable dust specimens from coal mines in United Kingdom; cytotoxicity index developed from effects on trypan blue exclusion, release of LDH, glucos-aminidase, and lactic acid production	A positive correlation between ash content and cytotoxicity of the dusts. In dusts with >90% coal, there was also a correlation between kaolin + mica content and cytotoxicity.
Macrophage-like cell line P338D ₁	Two kaolinites (KGa-1, KGa-2) from Source Clays repository, particle sizes 3.2 and 3.9 μm , with no cristobalite or quartz, incubated for 48 h	Cell viability not changed at 20 $\mu\text{g}/\text{ml}$, and 60-70% at 80 $\mu\text{g}/\text{ml}$.
Isolated human leukocyte	Cornwall kaolinite and four different illite clays	Kaolinite (5 $\mu\text{g}/\text{ml}$) caused 90% inhibition of the

elastase	(composition and particle size not specified), 5 µg/ml or 20 µg/ml	enzyme, illites (20 µg/ml), 10-53% inhibition.
Artificial organelles		
Liposomes (artificial phospholipid membrane vesicles ^b 0.1-2 µm diameter) entrapping dissolved chromate (CrO ₄ ²⁻)	Kaolinite, 90% <2 µm in diameter, at five concentrations, 0.1-10 mg/ml, incubated in cell suspension for 1 h	Dose-dependent loss of chromate from vesicles; loss of chromate after 1 h (in excess of spontaneous rate) approximately 20% with 10 mg/ml; spontaneous rate was 4-6%.

Apoptosis was measured in rat alveolar macrophage NR8383 cells challenged *in vitro* with respirable quartz or kaolin dust and with the dusts pretreated with dipalmitoyl phosphatidylcholine (DPPC) to model conditioning of respired dusts by interaction with a primary phospholipid component of pulmonary surfactant. NR8383 cells exposed to native quartz at concentrations from 50 to 400 µg/mL for 6 hr showed a dose-dependent increase in apoptosis measured by the TdT-mediated dUTP-fluorescein nick end labeling (TUNEL), cell death ELISA, and DNA ladder formation assays, while kaolin induced significant response only at the higher concentrations and only in the TUNEL and ELISA assays. For cell challenge from 6 hr to 5 days at 100 µg/mL of dust, quartz was active at all times while kaolin was active only at 5 days. DPPC pre-treatment suppressed quartz activity until 3 days and kaolin activity through 5 days. Cellular release of lactate dehydrogenase, measured in parallel experiments to compare dust apoptotic and necrotic activities, indicated that components of serum as well as surfactant may affect kaolin *in vitro* expression of those activities [Gao *et al.*, 2001].

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