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Chapter 11.5

CLAYS AND HUMAN HEALTH

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Clay minerals can be beneficial to human health by serving as active principles or excipients in pharmaceutical preparations, in spas, and in beauty therapy medicine. In some cases, however, these minerals can be harmful to human health. Both the beneficial and harmful effects of clay minerals are described in this chapter.

11.5.1. BENEFICIAL EFFECTS OF CLAYS AND CLAY MINERALS

A. Historical Background

Since prehistoric times man used clay for therapeutic purposes. There are indications that *homo erectus* and *homo neanderthalensis* used ochres mixed with water and different types of mud to cure wounds, to soothe irritations, as a method of skin cleaning, etc. This might be due to their mimicking animals, many of which instinctively use minerals for such kind of purposes. The clay plates of Nippur, Mesopotamia, which date back to about 2500 BC, contain a reference to the use of clay for therapeutic purposes, including the treatment of wounds and the inhibition of haemorrhages. In ancient Egypt, Pharaoh's doctors used Nubian earth as an anti-inflammatory agent, and yellow ochre (a mixture of clay and iron oxy/hydroxides) as a cure for skin wounds and internal maladies and as a preservative in mummification. Likewise, Cleopatra (44–30 BC), Queen of Egypt, used muds from the Dead Sea for cosmetic purposes (Bech, 1987; Newton, 1991; Robertson, 1996; Veniale, 1997; Reinbacher, 1999).

In the Ancient Greek period, mud materials were used as antiseptic cataplasms to cure skin afflictions, as cicatrices, or as a cure for snakebites. *Bolus Armenus*, a red clay found in the mountain caves of Cappadocia, old Armenia, present-day Turkey, was famous as a medicinal clay, as were the so-called *terras* of the Greek islands Lemnos, Chios, Samos, Isola, Milos, and Kimolos. These *terras* were prepared and

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shaped into disks (called "earth coins" and used until the 19th century) that were marked or stamped with different symbols, for example with the goat stamp, the mark of the goddess Diana/Artemis (Bech, 1987). Among these, the *terra sigillata* of Lemnos deserves particular mention, because of its astringent and absorbent properties. The clay from Kimolos was identified as Ca^{2+}-smectite (Robertson, 1986), and the *terra sigillata* of Samos as kaolinite or illite/smectite mixed-layer mineral (Giammatteo et al., 1997). Galeno (131–201 AD), a Greek doctor (born in Pergamo) described medicinal muds, and used clays to deal with malaria, and stomach and intestinal ailments.

In some civilisations, the use of clays was extended to ingesting clays for therapeutic purposes. Aristotle (384–322 BC) made the first reference to the deliberate eating of earth, soil, or clay by humans (for therapeutic and religious purposes). Later, Marco Polo described how in his travels he saw Muslim pilgrims cured fevers by ingesting "pink earth". This practice is still followed in certain countries and communities for therapeutic purposes, or even to relieve famine (Mahaney et al., 2000). The rubbing of clays into the body for therapeutic purposes was known for a very long time. However, this custom (as practiced in contemporary spa centres) did not become widespread in Europe until Roman times when dedicated buildings, called "balnea", were erected. Later, the use of spas declined. During the 19th century and the beginning of the 20th century spas reappeared, and were frequently visited. Many of them continue using muds for therapeutic purposes. Some examples are Centro Termal das Furnas in Vale das Furnas, on the island of São Miguel (Azores), Montecatini Terme, Ischia and Abano Terme in Italy, Karlovi Vary in the Czech Republic, and Archena and El Raposo in Spain.

The famous *Papyrus Ebers* (dated about 1600 BC, but a copy of a papyrus from 2500 BC) describes some diseases and their treatment using mineral- and, particularly, clay-based medicines. Other references to the curative powers of clays appear in *Pen Ts'ao Kang Mu*, a famous old catalogue about Chinese medicine. In Roman times similar references could be found in Dioscorides' *De Materia Medica* (60 BC). This book also has a section dealing with minerals and chemical substances used in pharmacy. In his *Natural History*, Pliny the Elder (23–79 AD) also described the use of clays, especially those found around Naples (volcanic muds), for curing stomach and intestinal ailments. In the 11th and 12th centuries Avicena (980–1037 AD) and Averroes (1126–1198 AD) classified and encouraged the use of medicinal muds (Bech, 1987; Veniale, 1999a). Later, *Lapidarios*, dealing partially with the use of minerals from a therapeutic perspective, would appear. Among these works is the famous *Lapidarios* of the Spanish King, Alfonso X the Wise (1221–1284 AD). The first extant *Lapidario* is a translation into Spanish by Yhuda Mosca and Garci Pérez of Abolays' book in Arabic that Abolays himself had previously translated from Chaldean, although its original source is not known (Brey Mariño, 1982). During the Renaissance *Pharmacopoeia* appeared. These were texts that, among other drugs, classify different minerals for medicinal uses. In addition, they described regulations concerning their uses, such as the official codes that must be followed to produce

medicines. Their appearance coincided with the first mineralogical classifications. In the 17th century the first scientific academies were founded, one aspect of whose work was to document the advances of mineralogy in medico-pharmaceutical matters, thus producing various entries in the pharmacopoeias. In the early 20th century the development of chemistry enabled numerous minerals to be obtained through synthesis. The use of synthetic minerals had a negative effect on the use of naturally occurring minerals for therapeutic uses and as excipients. However, given the difficulty and cost involved in synthesising minerals on an industrial scale, natural clay minerals are mainly used for such purposes at present. An exception is "Laponite S", a synthetic hectorite made by the Laporte Company (NL), and used as a jellifying material in cosmetic formulations (Galán et al., 1985; Bech, 1987; Carretero, 2002).

B. Clay Minerals in Pharmaceutical Formulations

The use of clay minerals in pharmaceutical formulations was described by many authors (Del Pozo 1978, 1979; Galán et al., 1985; Bech, 1987; Cornejo, 1990; Gámiz et al., 1992; Bolger, 1995; Veniale, 1992, 1997; Viseras and López-Galindo, 1999; López-Galindo and Viseras, 2000; Carretero, 2002), and collected in different pharmacopeias (AA.VV., 1996, 1998, 2002a,b,c,d).

Kaolinite, talc, palygorskite, and smectites are used for therapeutic purposes in pharmaceutical formulations as active principles or excipients. The possible use of sepiolite as active principle or excipient in pharmaceutical formulations was also investigated (Hermosín et al., 1981; Cornejo et al., 1983; Forteza et al., 1988; Ueda and Hamayoshi, 1992; Del Hoyo et al., 1993, 1998; Viseras and López-Galindo, 1999; López-Galindo and Viseras, 2000; Cerezo et al., 2001) and there are commercial medicine that includes sepiolite in its composition (as active principle and excipient). The fundamental properties for which clay minerals are used in pharmaceutical formulations are high specific area and sorptive capacity, favourable rheological characteristics, chemical inertness, low or null toxicity for the patient, and low price.

Use as Active Principles

As gastrointestinal protectors, antacids, and antidiarrhoeaics, clay minerals can be administered to the patient orally in the form of pills, powders, suspensions, and emulsions. Clay minerals are also applied topically (to the body's exterior, or on a limited portion of the body) as dermatological protectors or for cosmetic reasons.

Kaolinite and palygorskite are used as gastrointestinal protectors. Their therapeutic action is based on their high specific area and sorption capacity. They adhere to the gastric and intestinal mucous membrane and protect them, and can absorb toxins, bacteria, and even viruses. However, since they also eliminate enzymes and other necessary nutritive elements, their prolonged use is inadvisable. Although smectites also have a large surface area and sorption capacity, they are not generally used as gastrointestinal protectors. This is because smectites tend to decompose

when they come into contact with the stomach's hydrochloric acid (pH 2), and probably also when they get to the bowel (pH 6).

Smectites and palygorskite are used as antacid due to thin H^+ neuturalising capacity. They are indicated in the treatment of gastric and duodenal ulcers.

Kaolinite, smectites and palygorskite are also used as antidiarrhoeaics due to their high water adsorption capacity. By eliminating the excess water from faeces, the material becomes more compact. Calcium smectites are also used as antidiarrhoeaics due to the astringent action of the Ca^{2+} ion, which forms non-soluble, hydrated phosphates.

Kaolinite, talc, and smectites are used as dermatological protectors. These clay minerals can adhere to skin, forming a film that mechanically protects the skin against external physical or chemical agents. By absorbing the skin's secretions, and creating a large surface for their evaporation, they also have a refreshing action. Surface evaporation also promotes a gentle antiseptic action as it produces a water-poor medium that is unfavourable for the development of bacteria. This latter action is reinforced by the capacity of these minerals to sorb dissolved and suspended substances, such as greases, toxins, and even bacteria and viruses.

The use of these clay minerals as dermatological protectors should be preceded by a mineralogical study of the corresponding raw materials. This is because in many cases they contain mineral impurities such as quartz (in smectites), and chrysotile or tremolite (in talc) that are dangerous for inhalation. For example, Bowes et al. (1977) reported that of the 27 consumer talcum powders, purchased in the USA, 11 contained tremolite and/or anthophyllite in proportions ranging from 0.5 to over 14%. The use of palygorskite as a dermatological protector is not advisable. Nor does palygorskite appear in any pharmaceutical formulation as powder because of current doubts about its possible carcinogenic effect if inhaled (see below).

Kaolinite, smectite, talc, and palygorskite (the last one recommended only in liquid preparations such as creams, emulsions, etc.) are used as active principles in cosmetics. They feature in face masks because of their high capacity for adsorbing greases, toxins, etc. They are also used in creams, powders, and emulsions as antiperspirants, to give the skin opacity, remove shine, and cover blemishes. The 2002 market saw the appearance of a moisturising cream that contained very small particles of mica (possibly muscovite), producing a luminous, light reflective effect.

Use as Excipients

Kaolinite, talc, palygorskite, and smectites are used as excipients in cosmetics and pharmaceutical preparations. In the latter application, these minerals function as:

(i) lubricants to ease the manufacture of pills (talc);
(ii) agents to aid disintegration through their ability to swell in the presence of water (smectites), or through the dispersion of fibres (palygorskite), promoting release of the drug when it arrives in the stomach; and
(iii) emulsifying, polar gels and thickening agents because of their colloidal characteristics (palygorskite, smectites, kaolinite) by avoiding segregation of the

pharmaceutical formulation's components and the formation of a sediment that is difficult to re-distribute.

Although all the excipients are considered to be inert, research carried out during the last 30 years showed that interaction may occur between the drug and the clay mineral used (White and Hem, 1983; Sánchez Martín et al., 1988; Cornejo, 1990). This process can influence two highly important aspects in the drug's bioavailability: its liberation and stability. With respect to the drug's liberation, the interaction between the drug and its excipient can retard the drug's release and therefore its absorption, lowering its levels in the blood. This phenomenon, detectable by *in vitro* studies, may produce undesirable effects on a patient's health if, for the drug to be effective, immediate therapeutic levels in the blood are required, as in the case of antihistamines (White and Hem, 1983). However, the slow, controlled desorption of the drug can have a positive effect on its therapeutic action, as in the case of amphetamines and antibiotics (Mc Ginity and Lach, 1977; Porubcan et al., 1978), or water-resistant sun screens (Vicente et al., 1989; Del Hoyo et al., 1998, 2001). Regarding the drug's stability, interaction between drug and mineral excipient can accelerate degradation of the drug with consequent loss of therapeutic activity and increased health risk (Porubcan et al., 1979; Hermosín et al., 1981; Cornejo et al., 1983; Forteza et al., 1988, 1989).

The interaction of drugs with clay mineral excipients used in pharmaceutical preparations should be studied on a drug-by-drug basis. Doctors must also keep this point in mind when they prescribe medication to patients. Given the high surface reactivity of clay minerals, this interaction can occur either in the pharmaceutical formulation itself or in the gastrointestinal tract, even though the drugs are administered in different pharmaceutical formulations. This interaction can be detrimental to human health and, in some cases, to human life. For example, montmorillonite can catalyse the acid hydrolysis of digoxin, a cardiovascular tonic (Porubcan et al., 1979). When digoxin is administered in liquid preparation (without clay minerals), it can come in contact with montmorillonite from another pharmaceutical preparation administered at the same time. The interaction between digoxin and montmorillonite in the stomach (pH 2) could cause degradation of the drug. As a result, the drug loses its therapeutic activity and the patient's life is endangered.

C. Clay Minerals in Spa and Beauty Therapy

Kaolinite and smectites are used in spa and beauty therapy, as are illite, interstratified illite/smectite and chlorite, and, on occasion, sepiolite and palygorskite.

Common (polymineralic) clays are also used. Besides phyllosilicates, these minerals contain Fe-Mn-(hydr)oxides and other associated phases such as calcite, quartz, and feldspars. The presence of these phases should be controlled, because the final product applied to the patient should have only the required and appropriate mineral properties for their use.

The main properties of clay minerals determining their usefulness in spa and aesthetic medicine, are:

(i) softness and small particle size since the application of the mud, particularly as face mask, can otherwise be unpleasant;
(ii) appropriate rheological properties for the formation of a viscous and consistent paste, and good plastic properties for easy application, and adherence to the skin during treatment;
(iii) similarity in pH to that of the skin so as to avoid irritation or other dermatological problems;
(iv) high sorption capacity. Clays can eliminate excess grease and toxins from skin, and hence are very effective against dermatological diseases such as boils, acne, ulcers, abscess, and seborrhoea. An organic active principle can also be incorporated into the clay mineral before its application to the patient's skin for therapeutic purposes;
(v) high CEC, enabling an exchange of nutrients (K^+ or Na^+) to take place while the clay mineral is in contact with the skin; and
(vi) high heat-retention capacity. As heat is also a therapeutic agent, clay minerals are applied hot to treat chronic rheumatic inflammations, sport traumatisms, and dermatological problems.

Smectites (bentonite clays) fulfil many of the requirements for usage in spa and beauty therapy.

Types of Application and Therapeutic Activity

The different types of application and therapeutic activity of clay minerals in spas and beauty therapy received much attention over the past 20 years (Messina and Grossi, 1983; Torrescani, 1990; Barbieri, 1996; De Bernardi and Pedrinazzi, 1996; Novelli, 1996; Martín Díaz, 1998; Benazzo and Todesca, 1999; Lotti and Ghersetich, 1999; Nappi, 2001; Carretero, 2002).

Clays can be used mixed with water (geotherapy), mixed with sea or salt lake water or minero-medicinal water, and then matured (pelotherapy), or mixed with paraffin (paramuds). These three methods are used in spas and in beauty therapy. In geotherapy and pelotherapy the application form can be as face masks, cataplasms, or mud baths, depending on the body area to be treated, although in some spas they are also used for corporal massages. Application temperature (hot or cold) depends on the therapeutic aims. The paramuds are applied only as cataplasms, and always hot.

Face masks are used mainly in beauty therapy. Cataplasms are used in spas and in beauty therapy, when the mud is applied to only a small area of the body. Mud baths are preferentially used in spas, as the area under treatment is extensive. Application is carried out by submerging part of the body (bathing the arms, hands, or feet) or the whole body in a bowl or bath filled with a mixture of clay and water. The application of face masks and cataplasms is carried out in layers of between 1 and 5 cm for 20–30 min. When applied hot (40–45 °C) cataplasms are covered with an

impermeable material to conserve the heat. In most cases the paste is recycled from one patient to another.

Hot application is recommended in geotherapy, pelotherapy or paramuds in beauty therapy for the following therapeutic purposes:

(i) to moisturise the skin, since during application the perspiration produced cannot evaporate as the paste is covered with an impermeable material. This perspiration soaks into the upper layers of the epidermis, moisturising it from within. Moreover, after application, the skin is in a hyper-porous state, which means cosmetic substances will be easily absorbed by the corneous layer, reaching the deepest layers of the epidermis;
(ii) to treat compact lipodystrophies in their initial evolution when they need preventive care but cannot be treated more aggressively, and before the application of cosmetics;
(iii) to retard the development of cellulite, given that they stimulate venous and lymphatic circulation in the application area and that they act as anti-inflammatories; and
(iv) for cutaneous cleaning and treating dermatological conditions such as blackheads, spots, acne, ulcers, abscess, and seborrhoea. Heat promotes perspiration and the flow of sebaceous secretions in a fluid state, and their sorption by the clay mineral. Heat also opens the pylosebaceous orifices, improving sorption of the cosmetic substances.

Hot clay application produces a sensation of heat in the area treated, as well as vasodilatation, perspiration, and the stimulation of cardiac and respiratory frequency. As this creates a stimulatory, antiphlogistic, and analgesic action, such applications are recommended in spas, for the two following diseases: (i) chronic rheumatic processes including degenerative osteoarthrosis in any part of the body, dysendocrine arthropathies, spondilo-arthritis ankylopoietic, spondylosis, myalgias, neuralgias and (ii) sequelae of osteo-articular injuries, fractures, dislocations; disorders following vasculopathies.

We should note that hot application is contra-indicated in areas of the body with circulatory problems (e.g., varicose veins), and in the acute and sub-acute phases of rheumatic processes, discompensated cardiopathies, tuberculosis, and renal or hepatic deficiencies. In acute pathologies (inflamed or congested areas), the application temperature must be lower than body temperature (cold muds). Here the application produces a cooling of the area under treatment, and since the mixture is a good conductor of the heat given off by the inflammation, it acts as an anti-inflammatory agent. The mixtures can also be used cold in liquid-retention problems.

Pelotherapy

Of the three types of application of clay minerals in spas and beauty therapy, pelotherapy is the most favoured, because the maturation process improves the therapeutic properties of the final product (peloid) applied to the patient.

The International Society of Medical Hydrology defines "peloid" as "… a natural product consisting of a mixture of sea, salt lake, or minero-medicinal water (liquid phase), with organic and inorganic material (solid phase) produced by biological action (humus) and geological action (clay minerals)".

A comprehensive report on peloid preparation, particularly on the maturation process, is not available. However, much progress was made in this direction by the Gruppo Italiano of AIPEA who sponsored two meetings (Veniale, 1996, 1999b) and published a catalogue of Italian "clay geomaterials for peloids" (Veniale, 1999c). Since Italy has an exceptional tradition of thermal treatments, the catalogue and meetings provide a snapshot of pelotherapy, with about 30 spas collaborating to varied extents on compiling the catalogue. In recent years there were other important contributions to the knowledge of pelotherapy (Ferrand and Yvon, 1991; Veniale and Setti, 1996; Yvon and Ferrand, 1996; Veniale, 1997; Summa and Tateo, 1998; Bettero et al., 1999; Cara et al., 1999; Gorgoni et al., 1999; Jobstraibizer, 1999; Minguzzi et al., 1999; Summa and Tateo, 1999; Veniale et al., 1999; Cara et al., 2000a, 2000b; Sánchez et al., 2000a, 2000b; Gomes and Silva, 2001; Carretero, 2002; Sánchez et al., 2002).

Peloid preparation varies from place to place. Depending on the particular spa tradition, the maturation process ranges from a few months to two years. Some spas use naturally matured clays collected from a spring basin, others collect the peloid from saline pools. The majority of spas, however, use artificial ponds where the natural ("virgin") clay is mixed with mineral, thermo-mineral, or sea water that issues in the vicinity of the spas or inside the spa buildings. The clay is placed in the ponds for some months, during which period it is periodically shaken. The water may be stagnant, periodically renewed, or, more rarely, continuously flowing through the ponds. Interestingly, many spas initially used local clays but when these ran low, switched to commercial clays, or a mixture of local and commercial materials. An alternative strategy, adopted by some spas, is to recycle the material (after use on a patient), that is, the "exhausted" peloid is again matured. It is assumed that all harmful and hazardous elements, taken up from the previous patient, are removed during re-maturation.

Maturation is a very complex process involving water and a multiplicity of materials, including minerals (the mud is usually not mono-mineralic), inorganic solutes, biogenic components, and organic molecules as well as different physico-chemical conditions, such as temperature, Eh, and pH. Furthermore, many of these parameters are modified during the maturation period (cycling of temperature, light, hydrologic regime, shaking time). This can influence the manner in which certain materials develop. The length of maturation is a key parameter. The three main factors controlling peloid properties are raw clay composition, water composition, and mixing mode ("maturation"). During maturation organic substances as well as macro- and micronutrient elements present in the water are taken up by the peloid and can be released during application to the human body.

The maturation process improves some physical properties of the clay minerals, such as heat retention capacity, rheology, and adhesion. At the same time, some

changes in mineralogy and organic matter take place. These modifications improve the therapeutic effect of clay in pelotherapy.

With regard to specific heat, Ferrand and Yvon (1991) published a report on mixtures of clays. The thermal behaviour of several mixtures of kaolinite, bentonite, silt, and sand was tested and the temperature was measured at an appropriate and constant viscosity. The authors propose a lineal equation for the calculation of the specific heat, in function of the current in water. Likewise, Cara et al. (2000a) propose a similar formula to that of Ferrand and Yvon (1991) to calculate the specific heat of (Sardinian) bentonites. In agreement with the previous work, the specific heat was dependent on the smectite content of the bentonite. Although this investigation was not yet carried out with peloids (only with mixed water-clay, without maturation), the findings are important. By extrapolating the results to pelotherapy, heat dissipation during peloid treatment could be predicted.

The rheological and adhesive properties of peloids are important since the surficial interactions of skin with peloid drive the mass and heat transfer between the two bodies. Obviously, the nature of the raw material, the minero-medicinal water, and the maturation process have a profound influence. A number of parameters were recently used to measure the characteristics of the muds and their affinity to the skin. Bettero et al. (1999) used the RTM® and TVS® indices. The RTM® index represents the evolution of the viscous, elastic, visco-elastic, and structural features of the mud, whereas the TVS® is a bioadhesive index, representing the affinity of different materials (mud, water, etc.) for the surface of the skin in question. Both indices can be used to predict peloid quality obtained through a given maturation process. Sánchez et al. (2000b) used the adherence index, a measure of the adhesiveness of the peloid to the skin, and found that this index did not vary with the maturation time (one clay, two different waters). However, these results cannot be extrapolated to all spas (with different composition of the waters and clay mineralogy), and further investigation in this field is necessary.

While the rheological properties of various clay minerals were long investigated in relation to different applications (Güven and Pollastro, 1993; Penner and Lagaly, 2001), not much research was carried out in terms of pelotherapy. It seems likely, however, that the rheological and adhesive properties of therapeutic clays can be "tuned" to their mineralogical composition and maturation conditions.

Little information is available about the clay mineral composition in peloids and the changes in mineralogy that occur during maturation. There are some pioneering papers on the topic, and others are concerned with spas that use fast methods of maturation, or those that are developed by the authors themselves. Since the number of publications dealing with clay mineralogy is limited, and the results are not always consistent, no general trends can be outlined, and more research is needed. Differences in results can be due to the different raw materials and water composition used in maturation. For example, in maturing an illitic–smectitic clay in a ferruginous-bicarbonate-sulphate water (pH 6.4), Sánchez et al. (2002) found that the content of smectite (and $<2\,\mu m$ fraction) decreased after three months. This finding was

explained in terms of degradation of the illite–smectite as indicated by a decrease in the mineral's crystallinity. An improvement in the quality of the muds was indicated by an increase of the plasticity index and a slowing of the cooling rate. Similarly, Veniale et al. (1999) observed an increase in the Atterberg plastic and liquid limits (the latter implying a decrease in cooling rate). On the other hand, the granulometric results showed the opposite trend to that reported by Sánchez et al. (2002). However, since different raw materials and maturation water were used by both groups, different mineralogical changes would occurred. Thus, maturation with the water used by Sánchez et al. (2002) led to a reduction in the smectite content. Veniale et al. (1999) reported that sulphurous water degraded some constituents of the starting clayey admixture (chlorite, illite/smectite, and feldspars) into smectite, while bromic-iodic-salty water transformed smectite into an "intergrade" and/or chlorite. In investigating the composition of two matured muds from different spas, Summa and Tateo (1998) also found that maturation led to a decrease in grain size, while both mineralogy and chemistry were almost unchanged. In addition, these authors observed that some ultratrace elements could be leached by water after maturation but not before. Likewise, Minguzzi et al. (1999) detected little change in mineralogy and chemistry (two spas considered) although the thermal behaviour of carbonate minerals is greatly altered in one case. Therefore, until investigation advances in this field, it is advisable to study the effects of maturation in the raw material, using water specific to each spa.

The qualitative determination of organic substances in peloid is well documented (see Curini et al., 1990). Jobstraibizer (1999, 2002) observed an increase in the content of organic matter and diatoms as maturation progressed, but only in the case of virgin clays, whereas the recycled muds seemed already in equilibrium with the maturing environment. Galzigna et al. (1996) reported that sulphoglycolipid (a powerful anti-inflammatory agent produced by diatoms) developed immediately after the drop in chlorophyll α concentration, at about one month of maturation in sulphate-Br-I waters. An increase in organic matter content following maturation was also observed by Curini et al. (1990), but only for two of the three spas investigated. On the other hand, the increase in diatoms and organic materials obtained by Jobstraibizer (2002) was accompanied by a rise in exchange capacity and plasticity although the peloid in question was low in clay minerals and contained little smectite.

Finally, it is always advisable to assess the potential risks to human health of the peloids applied in each spa, because they occasionally contain hazardous elements that may be released during application. These elements can occur in the clay (and associated phases in clay), or in the minero-medicinal water. For example, Summa and Tateo (1998) found that sweat, produced during typical pelotherapy, can extract trace amounts of hazardous chemical elements from matured peloids. Some of these elements (As, Se, Tl) probably come from the maturation water, rather than being intrinsic to the pristine clay. Obviously, the toxicological aspects of pelotherapy are the concern of specialists (as Bressa and Cima (1999) described in the case

of Italy) but clay scientists and geochemists must play an active role in assuring peloid quality.

The possibility that some peloids could be radioactive must also be borne in mind. The water of many spas (for example, more than 25 Spanish spas) is radioactive, and hence fundamentally useful for treating rheumatic problems. The radioactive elements of most therapeutic interest in minero-medicinal waters are isotopes of radio-uranium, uranium–actinium, and thorium. The radio-uranium isotopes, ^{226}Ra and ^{222}Rn, and their disintegration products are the most therapeutically important (San José Arango, 2001). Radioactive elements, incorporated in the peloid during maturation, can be beneficial to human health. In some cases, however, the quantity of radioactive elements absorbed by clay minerals could be so high as to be harmful to health, particularly if the material is recycled.

Gorgoni et al. (1999) pointed out that most spa centres are built in the vicinity of springs (or exactly over them), and hence are vulnerable to Rn contamination. The deeper the spring, the longer it takes for the water to reach the crust, and the higher is the probability of Rn accumulation (before emergence). At high concentrations radon is dangerous because it emits ionising radiation, is volatile, and can be inhaled (Committee on Health Risks of Exposure to Radon, 1999). Inside the lung radon quickly disintegrates, giving rise to a radioactive solid (^{218}Po). This material remains permanently in the lung because it is not volatile as Rn is. The solid begins a disintegration cycle by emitting alpha and beta particles within minutes. The resultant damage to lung cells can cause lung cancer. Because the affinity of Rn for solid substances is very low, Rn hazard does not appear to be directly associated with peloids but with pelotherapy in a general sense. A different consideration applies to spas that recycle the peloid. In this case, the exhausted mud may retain some radioactive elements, the concentration of which would increase during repeated recycling.

11.5.2. HARMFUL EFFECTS OF CLAYS AND CLAY MINERALS

A. Background Information

The harmful effects of some minerals on human health were known for centuries. In his medical writings Hippocrates (460–355 BC) referred to the metal digger as a man who breathed with difficulty. Later, Pliny the Elder (23–79 AD) described illnesses associated with exposure to Hg sulphide dust. By the Middle Ages, illness caused by mineral dust was sufficiently recognised to be mentioned by Agricola, in *De Re Metallica* (1556):

> " … Some mines are so dry that they are entirely devoid of water and this dryness causes the workmen even greater harm, for the dust, which is stirred and beaten up by digging, penetrates into the windpipe and lungs and produces difficulty in breathing … . It eats away the lungs and implants consumption in

> the body … . In the mines of [the] Carpathian Mountains women are found who married seven husbands, all of whom this terrible consumption carried off to a premature death".

Agricola also recorded that the miners at Joachimstal, Bohemia, used gauze masks in order to obtain some relief and protection. This report is certainly one of the earliest references to respiratory protection equipment (Chisholm, 1994).

Mineral dusts cause damage by inhalation, and rarely by ingestion, or ingress into the skin. In the lungs the minerals can produce diverse pathologies: (i) lung cancer; (ii) mesothelioma (mesothelial cancer); and (iii) pneumoconiosis (the lung becomes fibrous and loses its capacity to work). Mineral pathogenicity can be determined by epidemiological studies (evaluating the relationships between human exposure to a hazardous substance and the potential health effects), *in vivo* studies (animal models are used extensively to study the effects of exposure to mineral dusts), and *in vitro* studies (specific cells are used to determine a mineral's biolgical activity) (Guthrie, 1992).

In most biological experiments particle shape and particle-size distribution, together with mass concentration or dose employed, are generally controlled, since these parameters appear to relate to the material's biological activity. However, the exact mineral composition (type and content) of the dusts is rarely characterised. In other words, little attention is generally paid to the identification and quantification of contaminants in the dust sample. Instead, it is assumed that the mineral composition of the sample accords with the information provided by the supplier. However, samples obtained from most suppliers potentially contain a mixture of minerals. Another mineralogical problem in biological studies is that the surface properties of the samples are generally not adequately characterised, given that the toxicity of minerals relates to their surface state and surface area, which in turn can vary substantially between samples. These mineralogical deficiencies in biomedical research can be rectified through collaborative efforts between toxicologists, biomedical experts, chemists, geologists, and mineralogists (Guthrie, 1992; Santaren and Alvarez, 1994; Wagner et al., 1998).

Particle dimensions and surface properties, as well as mobility in the respiratory system determine the depth to which particles may penetrate the lung. In general, particles with aerodynamic diameters greater than about 10 μm impact on the upper reaches of the respiratory tract, and are rapidly moved up the bronchioles by specially adapted cells that sweep the particles towards the throat. These particles are then cleared and expectorated or swallowed. Particles with equivalent spherical diameters of 1–2 μm would deeply penetrate the alveolar regions of the lung. Since the body's natural clearance processes in the deep lung are not efficient, these particles tend to remain in the alveolar walls. As a result, gas exchange across the alveolar membrane is reduced.

Mineral dusts are cleared from the lung by several different mechanisms, including exhalation of suspended particles, sequestration of particles by macrophages, relocation via the mucocilliary escalator and the lymphatic system, *in situ* dissolution, or

a combination of these mechanisms (Brown et al., 1991; Lehnert, 1993). Since macrophages cannot completely engulf mineral fibres that are longer than the cells themselves, there is incomplete phagocytosis of fibres, and irreversible cell damage and death can occur (Kane, 1991). Stanton et al. (1981) established that the optimum dimensions for the induction of intrapleural tumours is a diameter $\leqslant 0.25\,\mu m$ and a length $> 8\,\mu m$. However, Nolan and Langer (1993) showed that the "Stanton hypothesis", relating a fibre's morphology to its activity for the induction of tumours, has some limitations. Other studies defined the critical fibre dimensions for lung cancer and mesothelioma as $< 0.3–0.8\,\mu m$ in diameter and $> 10–100\,\mu m$ in length for lung cancer, and $0.1\,\mu m$ in diameter and $> 5–10\,\mu m$ in length for mesothelioma (Harington, 1981; Lippmann, 1988). Pott (1989) showed that fibre pathogenicity not only depends on the dimensions of the fibre, but also on its persistence in the lung.

Currently, the important factors influencing the health hazards of minerals are considered to be (i) site of ingress to body (skin, ingestion, inhalation); (ii) type of response (irritation, fibrosis, cancer); (iii) duration of exposure to the particles; (iv) particle size; (v) morphology of thin asymmetrical fibres with diameters $< 0.25\,\mu m$ and lengths $> 8.0\,\mu m$; (vi) composition, including high iron content; (vii) low solubility at low pH; (viii) value and sign of the surface potential; (ix) hydrophobicity vs. hydrophilicity; (x) *in vitro* activation of phagocytic leukocytes; and (xi) generation of hydroxyl radicals that can break the DNA strand which constitutes the initial step in genotoxicity and cancer (Gilson, 1977; Bates et al., 1989; Bignon, 1990; Brown et al., 1991; Guthrie, 1992; Guthrie and Mossman, 1993; van Oss et al., 1999). Using factors (v), (vii), and (x) van Oss et al. (1999) classified mineral particles as Category I (exceedingly dangerous), or Category II (dangerous after continuous and protracted exposure). For both categories, the onset of overt disease in humans usually occurs after one to several decades. It should also be noted here that the mineral dust risks are closely related to cigarette smoking. For the same period of mineral dust exposure, smokers are more likely to be affected than non-smokers.

The two main illnesses related to mineral dust exposure and inhalation that produced most human deaths in history are silicosis and asbestosis. Silicosis (a pneumoconiosis type), caused by exposure to quartz particles, was widespread during the Industrial Revolution as quartz was a major component of many raw materials used in many processes. Thus, the growth of the iron and steel industry led to increased use of sand for casting, and of sandstone for grinding edge tools and fettling metal casting (Winkler, 1975; Chisholm, 1994). Asbestosis is a serious illness caused by the inhalation of asbestos. "Asbesto" is a commercial name for fibrous minerals including (i) fibrous amphiboles such as actinolite, tremolite, crocidolite (blue asbesto), and amosite (brown asbesto) and (ii) serpentine species notably chrysotile (white asbesto). The dust of these minerals produces lung fibrosis that can develop into lung cancer or mesothelioma. Asbestos clothes were mentioned by Charlemagne (747–814 AD) and later by Marco Polo (1254–1324 AD). Having its beginnings in the 1850s, the asbestos industry grew rapidly from the 1890s onwards

in Europe and the USA (Bowes et al., 1977; Chisholm, 1994). As a result, asbestosis spread widely during the 20th century. References to the harmful effects of quartz and asbestos can be found in the papers by Bowes et al. (1977), Gilson (1977), Germine and Puffer (1989), Brown et al. (1991), Guthrie (1992), Hume and Rimstidt (1992), Guthrie and Mossman (1993), and BéruBé et al. (1998).

Although quartz and asbestos are the most harmful for human health, clay minerals could also be dangerous because of their limited solubility in the lung, reactivity, small particle size, and fibrous habit (as in the case of sepiolite and palygorskite).

B. Pathogenicity of Clay Minerals

Although clay minerals could, in some cases, be dangerous when ingested (Mascolo et al., 1999; Tateo et al., 2001), the pathogenicity of clay minerals is mainly caused by inhalation. There are investigations about the pathogenicity of kaolinite, talc, sepiolite, palygorskite, illite, and smectites (montmorillonite). The possible pathogenicity of these clay minerals was reviewed by Bignon (1990), Hollinger (1990), Guthrie (1992), Davis (1993), Ross et al. (1993), Santaren and Alvarez (1994), Governa et al. (1995), Galán (1996), Wagner et al. (1998), and Jurinski and Rimstidt (2001).

The results of these investigations are contradictory. Most epidemiological studies indicate that clay minerals are only dangerous for human health when exposure time is very long, and toxicity is generally related to the presence of quartz or asbestos in mining. For example, chrysotile and tremolite are commonly associated with talc, quartz with kaolinite, quartz and amphiboles with illite and smectites, etc. *In vivo* and *in vitro* studies , however, indicate that these minerals can be harmful, although in many cases the initial sample was not pure but was contaminated with quartz or asbestos.

For example, Adamis and Timar (1980) reported that bentonite, illite, and three out of four kaolin samples were all cytotoxic *in vitro* but could not find a relationship between their quartz content and their harmful effect. Guthrie (1992) indicated in his review that most samples containing 1:1 clay minerals can produce fibrosis or tumours *in vivo* and can be highly active *in vitro*. Some samples with 2:1 clay minerals, can produce fibrosis *in vivo* and can be highly active *in vitro*. However, epidemiological data suggest fibrosis may not be a problem under modern mining conditions. Clay minerals can be cleared rapidly from the lung, and hence are not pathogenic in humans. Their activity may therefore provide clues to the mechanisms of mineral-induced pathogenesis. Wagner et al. (1998) suggested that changes to the lung only result from prolonged (in excess of 20 years) heavy exposures to clay minerals, since they are weakly fibrogenic. These workers are concerned only with inflammatory and fibrotic responses since exposures to clay minerals are not associated with the development of malignancies unless the samples are contaminated with such minerals as quartz and asbestos.

The pathogenicity of sepiolite and palygorskite is related to geological formation conditions since these determine fibre length and particle crystallinity.

The main harmful effects of different clay minerals are discussed below.

Kaolinite

The harmful effect of kaolinite is mainly related to the presence of quartz since kaolinite-bearing rocks generally contain variable amounts of other minerals including quartz. Kaolinite workers who were heavily exposed to kaolinite dust may develop pneumoconiosis, often referred to as kaolinosis. An increased lung cancer risk was not reported in kaolinite workers (Ross et al., 1993).

Epidemiological studies, reviewed by Guthrie (1992), suggest that kaolinite-bearing dust is fibrogenic only under extraordinary conditions, notably high concentrations of dust or exposure combined with another respiratory disease, such as tuberculosis. Lapenas et al. (1984) found kaolinite in the pulmonary tissue of five kaolin workers who had pneumoconiosis but did not detect silica in the lung samples. Similar findings were reported by Davis (1993).

The results of i*n vivo* experiments on the fibrogenic potential of kaolinite-bearing dusts are inconclusive. For example, Mossman and Craighead (1982) found that kaolinite (3–5 μm in diameter, Georgia Kaolin Company) does not induce tumours in golden Syrian hamsters following subcutaneous implantation of *in vitro*-exposed tracheas. Inhalation experiments by Wagner (1990) produced no lung tumours in 20 rats exposed over a period of 3–24 months although a slight fibrogenic response was observed. However, the samples contained 85–95% kaolinite, with the remainder consisting of mica, feldspar, and quartz. Davis (1993) has suggested that the differences in results between experimental inhalation studies with kaolin dusts are due to differences in the dosage used. Likewise, Wagner et al. (1998) indicated that kaolinite is mildly fibrogenic.

In vitro experiments show that some kaolinite-bearing samples are cytotoxic to most cell types. For example, kaolinite is cytotoxic to rabbit alveolar macrophages (Low et al., 1980) or mouse peritoneal macrophages (Davies, 1983), but is much less cytotoxic to guinea pig peritoneal macrophages than silica minerals (Marks and Nagelschmidt, 1959). The cell-damaging capacity of kaolins can vary markedly from sample to sample, presumably because of variations in mineralogical properties (such as crystallinity) among deposits, and the presence of varied quantities of other minerals, particularly types of silica. As a result, investigations carried out at about the same period of time can show different results. Thus, the pure kaolin samples studied by Robertson et al. (1982) were markedly cytotoxic whereas the two kaolin samples used by Gormley and Addison (1983) were essentially non-cytotoxic. Further, Daniel and Le Bouffant (1980) reported a low cytotoxicity for kaolin, while Low et al. (1980) suggested that kaolin is cytotoxic to alveolar macrophages by causing membrane damage, similar to that proposed for other silicates.

Talc

Chronic exposures to high concentrations of talc were associated with the development of talcosis, a type of pneumoconiosis. There were numerous health studies of talc workers, but their results were often ambiguous.

In general, epidemiological studies suggest that exposure to talc-bearing dusts elicits a dose-dependent response. Serpentine minerals, including chrysotile, are commonly associated with talc in ultramaphic source rocks, while tremolite commonly occurs with talc in metamorphosed carbonate rocks (Bowes et al., 1977; Davis, 1993). Therefore, talc miners are exposed to dusts other than talc, and it is not possible to assign the results of epidemiological studies to talc exposure alone. Ross et al. (1993) indicated that talc workers exposed to talc dust may exhibit symptoms of talc pneumoconiosis. Several epidemiological studies of talc workers are in disagreement as to whether talc causes lung cancer. Excess cancer may be related to underestimation of smoking habits or to previous exposure to commercial asbestos. Epidemiological studies of talc workers have not provided conclusive evidence that talc is carcinogenic. This is because the number of workers studied was not large enough to produce statistically significant data, smoking habits were not well defined, and the workers were often exposed to other mineral dusts. There is no doubt, however, that heavy exposure to talc dust can cause non-malignant respiratory disease.

In vivo experiments on talc-bearing dusts suggest that talc is non-fibrogenic and non-carcinogenic. *In vitro* experiments are inconclusive about the cytotoxic activity of talc-bearing dusts (Guthrie, 1992). Talc is much less hemolytic than kaolinite or montmorillonite (Woodworth et al., 1982). Experimental studies by Davis (1993) demonstrated that talc dust possesses only a low level of pathogenicity but this result is not borne out by other studies. For example, Hollinger (1990) suggested that the pulmonary toxicity of talc for babies, who somehow inhale excessive amounts, can be severe and lasting. Talc, used inappropriately and intravenously, can produce microemboli in small pulmonary vessels, leading to various degrees of tissue granulation, compromise pulmonary function, or death. This fits well with the preferential transport by phagocytes of insoluble particles to the lungs. Talc, with low solubility, and a particle shape and dimension allowing for complete phagocytic engulfment, can produce leukocyte activation and would be more dangerous than silica (van Oss et al., 1999). However, industrial exposure to silica is typically much longer than exposure to talc. Jurinski and Rimstidt (2001) measured the dissolution rate of a well-characterised sample of powdered talc, and estimated a lifetime of about eight years for a 1-μm talc particle under pulmonary conditions. Talc dissolves in the body considerably faster than quartz, but slower than chrysotile. These authors suggested that mineral durability does not seem to be a major factor in the development of pulmonary disease, since biodurability does not appear to correlate with the disease-causing potential of mineral dust exposures.

Sepiolite and Palygorskite

Epidemiological studies of sepiolite and palygorskite workers showed that exposure to sepiolite-bearing dust does not increase the risk of pulmonary disease. There is no evidence of pleural plaque and no reported mesothelioma. Therefore, exposure to these minerals does not present any risk (Baris et al., 1980; Guthrie, 1992; O'Driscoll, 1992; Mc Connochie et al., 1993; Ross et al., 1993; Santaren and Alvarez, 1994).

In vivo and *in vitro* studies indicated that, in some cases, sepiolite and palygorskite could be dangerous for human health. Health hazards depend mostly on the type of deposit and its geological formation conditions, which determine fibre length and particle crystallinity.

Wagner et al. (1987) carried out intrapleural tests with sepiolite in rats, and found no increased incidence of tumours. Similar results were obtained with rats inhaling sepiolite and palygorskite. These minerals did not produce fibrosis but only an interstitial reaction similar to that caused by nuisance dust.

In vivo studies of palygorskite suggested that most palygorskite-bearing dusts are mildly active in the lung, though some samples can be very active (Guthrie, 1992). *In vitro* experiments indicated palygorskite is as hemolytic as chrysotile, but in other non-erythrocyte cell types palygorskite is non-genotoxic and, at most, only slightly cytotoxic. The lysis of erythrocites was studied by Oscarson et al. (1986) who found sepiolite and palygorskite to be lysing agents. The edge surfaces and silanol groups of the minerals are important to the lysing process, whereas their elongate particle morphology appears to be irrelevant.

However, Wagner et al. (1987) provided evidence to show that inhalation by rats of sepiolite and palygorskite, containing a significant number of fibres greater than 5–6 μm in length, produces mesothelioma. Pott et al. (1990) carried out an intraperitoneal injection study with a sepiolite from a geological deposit in Finland. The mineral was formed under hydrothermal conditions, allowing for the development of a high degree of crystallinity. In causing a high incidence of tumours, this sample of sepiolite was classified by Pott (1989) as "probably carcinogenic". Koshi et al. (1991) studied the biological activity of sedimentary and non-sedimentary sepiolites with different crystallisation grade and particle length. Well-crystallised sepiolite with long particles showed strong cytotoxic and genotoxic effects. Chamberlain et al. (1982) also found a relationship between fibre length and cytotoxicity for sepiolite and palygorskite. Nolan et al. (1991) reported that the *in vitro* activity of palygorskite varies between samples. Among nine palygorskites with varied surface characteristics they found a corresponding range in hemolytic activity. Davis (1993) suggested that samples with fibres > 5 μm in length were harmful, whereas materials consisting entirely of short fibres were not. To determine the possible pathogenicity of sepiolite from Vallecas-Vicalvaro (Spain), Santaren and Alvarez (1994) reviewed the epidemiological data on both *in vivo* studies with different methods of administration (inhalation, intrapleural injection, and intraperitoneal inoculation) and *in vitro* studies. The results were consistently negative, showing a low intrinsic biological activity and an absence of exposure-related diseases. The conclusion is that sepiolite from Vallecas-Vicalvaro is not carcinogenic and the only effects that can be expected from this material are the same as for other non-fibrous nuisance dusts.

Illite and Smectites

Only a few epidemiological studies of respiratory disease resulting from exposure to dusts containing illite and smectites were published. Some studies suggested that

such samples can elicit a mild, dose-dependent fibrogenic response at high exposure levels. Generally, however, there is a concomitant exposure to other minerals (e.g., silica and amphiboles), and the response to these minerals complicates the interpretation of the data. For example, bentonite deposits generally contain other minerals, including very fine-grained quartz and amorphous silica. In the case of Wyoming bentonites, the silica content (which included both quartz and cristobalite) ranges from 0 to 24% (Ross et al., 1993).

In vivo experiments suggest that samples containing these minerals are slightly fibrogenic, and *in vitro* experiments indicate that they may be slightly cytotoxic (Guthrie, 1992). Gormley and Addison (1983) studied three different samples of montmorillonite. Although the materials show different cytotoxicities, much of the variability is apparently due to SiO_2 polymorphs. However, most other montmorillonite samples proved to be very cytotoxic *in vitro* (Daniel and Le Bouffant, 1980).

Lysis of bovine red blood cells (erythrocytes) by some silicate minerals was studied by Oscarson et al. (1986). The hemolytic activity of these minerals decreases in the order smectites > silica > palygorskite $\approx$ sepiolite > chrysotile > kaolinite. These *in vitro* studies showed that the reaction is complete in less than 1 h when the mineral surfaces became saturated with cellular components and lost their lytic activity.

11.5.3. CONCLUDING REMARKS

In pharmaceutical formulations, spas and beauty therapy, clay minerals are used for therapeutic purposes and their beneficial effect on human health. In pharmaceutical formulations these minerals are used as active principles (gastrointestinal protectors, antacids antidiarrhoeaics, dermatological protectors, cosmetics) and excipients (inert bases, delivery systems, lubricants, emulsifiers). In spas and beauty therapy clay minerals are used in geotherapy, pelotherapy, and paramuds, to treat dermatological diseases, alleviate the pain of chronic rheumatic inflammations, moisturise the skin, and combat compact lipodystrophies and cellulite.

However, clay minerals can also have an adverse effect on human health when they are inhaled over a very long period. In the lung, clay minerals can cause diverse pathologies such as cancer, mesothelioma, or pneumoconiosis, but the toxicity of these minerals is generally related to the presence of quartz or asbestos from mining operations. The pathogenicity of fibrous clay minerals (sepiolite and palygorskite) is related to the geological conditions of formation.

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