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**SCIENTIFIC COMMITTEE ON MEDICINAL  
PRODUCTS AND MEDICAL DEVICES**

**Opinion  
On  
Toxicological Data on Colouring Agents for Medicinal Products:  
E 174 Silver**

**Adopted by  
The Scientific Committee on Medicinal Products and Medical Devices  
On 27 June 2000**

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***Toxicological Data on Colouring Agents for Medicinal Products:***  
***E 174 Silver***

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## **Question**

The DGIII has asked the Scientific Committee for Medicinal Products and Medicinal Devices (SCMPMD) to express its opinion on the suitability/safety of the “colours permitted for certain uses only” listed in Annex IV of EEC 94/36 [in particular: E 123 (Amaranth) E 127 (Erythrosin); E 161 (Canthaxanthine); E 173 (Aluminium); E 174 (Silver); E 175 (Gold)] for use in pharmaceutical products and the question of whether the use of these agents might represent a consumer health/safety concern.

The question to be examined by the SCMPMD regards the following colourant:

### ***E 174 Silver***

## **Answer**

Silver is currently banned as an orally administered drug: it may be used only for preparations applied topically to the skin or mucosa. However, Annex IV of Directive 94/36 allows “*quantum satis*” use of this metal as a coloring agent in foods and beverages, and certain “health food” products currently on sale in the United States can provide daily oral doses of the metal ranging from 5 to 30 µg.

Potential exposure to silver used as a coloring agent in medicinal products by oral route has to be added to that ingested daily with food and water, and both types of exposure are extremely difficult to quantify. Therefore, it is the Committee’s opinion that use of this metal as a colorant be prohibited in medicinal products.

## **Main elements of the scientific justification of the answer**

The amount of silver that can be safely consumed by humans (i.e., the reference dose, RFD) is 5 µg/kg/die (approximately 350 µg). Two liters of drinking water / day would already provide around 200 µg of silver. An additional 10-25 µg / day would be ingested with milk, which contains 27-54µg / L, and the metal is found in variable quantities in a number of other foods as well, e.g., mushrooms, which can contain hundreds of micrograms of silver per gram.

Considering the data on silver toxicity, use of the metal as a coloring agent in medicinal products might be acceptable for the time being, but its use should be banned.

## **Opinion**

According to Annex IV of Directive 94/36, Silver (E. 174) can be used *quantum satis* to color both food and beverages, and the metal can also be ingested in the form of dietary supplements sold in “health-food” shops. The presence of silver (E. 174) as a coloring agent in medicinal products (which are often used for relatively short periods) may in itself represent an acceptable level of exposure. However, considering the amount of silver that can also be ingested with food (which is extremely difficult to predict) and the low reference dose recommended for humans, the Committee feels that this use should be banned as a colorant in medicinal products.

## **Full opinion**

### **Terms of reference**

The SCMPMD has been asked to respond to the following question:  
Would use of colourants listed in Annex IV ("colours permitted for certain use only") of Directive 94/36 (in this case E174 Silver), in medicinal products represent a consumer health/safety concern?

### **Context of the question**

EEC Directive 78/25, which deals with colouring agents that can be used in medicinal products, makes reference to the Directive issued on 23 October 1962 regarding colouring agents in food (OJL 115 f 11.11.1962 p. 2645). However, the EEC policy on food-colouring agents has been updated since then by Directive 94/36. Of particular interest in the latter document are Annex I, which lists all substances approved as food colourants, and Annex IV, which contains 10 such agents whose use is restricted to certain foods.

The pharmaceutical industry is questioning the scientific justification for excluding the use of Annex-IV colourants in medicinal products, citing in particular the clause in EEC Directive 78/25 that states, "Experience has shown that on health grounds there is no reason why the colouring matters authorised for use in foodstuff intended for human consumption should not also be authorised for used in medicinal products".

### **Assessment**

The question must be evaluated in relation to: 1) the maximum quantities and concentrations/unit of weight in foodstuffs, 2) those currently found in pharmaceutical products as active principle or excipient, and 3) the toxicological characteristics of the element.

E 174 (Silver) is used to decorate cakes, candies, and other sweets, and Annex IV of Directive 94/36 allows unlimited use (*quantum satis*) of this colourant in foods.

The standards for purity regarding E 174 (Silver) are reported in EC Directive 94/45 of the 26 July 1995 Commission, which deals with colourants that can be used in foods. The Directive notes that silver presents as a powder composed of finely ground particles of the metal. The metal can also be transformed into ultra-thin sheets or films.

### ***General considerations***

Silver (Ag) is a metal that is widely distributed throughout the earth's crust. It is found in both sea water and fresh water, in the soil and rocks; it is even present in the air as a result of industrial pollution. Silver is also used as a disinfectant for drinking water. According to the United States Environmental Protection Agency (1991a), the RFD that is "unlikely to be associated with an appreciable risk for deleterious effects during a lifetime" (in the general population, including members of sensitive subgroups) is 5 µg/kg/day, and the "critical" dose for man is estimated to be 14 µg/kg/day. The maximum concentration allowed in drinking water is < 0.1 mg/L (US Environmental Protection Agency, 1991b). Based on the currently accepted Rfd, maximum daily exposure to silver should be less than 25-350 µg. A person who drinks two liters of water a day ingests ~ 200 µg of silver, but since the metal is also found in a number of foods, dietary exposure can be expected to add at least another 90 µg (Clayton and Clayton, 1981; Tipton et al., 1966; Hamilton and Minaki, 1972). Refined wheat flour, for example, contains 0.3 µg/g, wheat bran 0.9 µg/g, milk 27-54 µg/L (Hamilton and Minaki, 1972), and mushrooms hundreds of µg/g (Fung e Bowen, 1996).

### ***Silver in pharmaceutical products***

Today, many of the previous therapeutic uses of silver have been abandoned, e.g., oral administration of silver nitrate for epilepsy, intravenous administration of silver arsphenamine for syphilis, colloidal silver preparations for various infectious diseases. The United States Dispensary of 1960 states that "there is no justification for this (internal) use either theoretically or practically." More recently, the United States banned all over-the-counter drugs containing silver.

Nonetheless, silver is still used in topical medicinal products. Silver nitrate, for example, is used as a 1% solution for the prevention of gonorrhoeal ophthalmia neonatorum, and solutions of 10-75% are employed for their necrotizing effects on warts and corns. Silver carbonate is a bland disinfectant.

The colloidal silver proteins (CSP) are prepared by mixing silver nitrate, sodium hydroxide, and gelatin, which interact to form a complex colloidal aggregate. The latter can then be diluted with water to the desired concentration. There are two types of CSPs: the Mild Silver Proteins (19-23% Silver) and Strong Silver Protein (7.5-8.5% Silver). In the mild silver proteins, there are higher concentrations of silver, but it is less subject to ionization. These products act as bacteriostatic disinfectants and produce minimal irritation. They were once used to disinfect the mucosa of the colon, the urethra, nose, and throat, but today their use is limited to the nasal and oropharyngeal mucosa. The concentration of silver in the Strong Silver Proteins is lower, but the metal is more subject to ionization. Strong Silver Proteins are irritating substances and probably exert bactericidal effects (Fung e Bowen, 1996).

Colloidal silver compounds act by releasing metallic silver, which is a potent caustic that binds to the reactive groups of proteins (sulfhydryl, amine, carboxyl, phosphate, imidazole), provoking rapid protein denaturation and precipitation (Fung and Bowen, 1996). Silver is also a powerful antibacterial agent. Wysor and Zollinhofer (1973) suggested that silver sulfadiazine is a potent bactericidal, unlike silver nitrate, which is merely bacteriostatic. Silver also forms complexes with DNA without causing aggregation or destruction of the double helix (Zavriev et al., 1979; Yakabe et al., 1980), and it is a potent inhibitor of fungine DNase (Saruno et al., 1979). Shinogi and Maeizumi (1993) also found that silver is capable of stimulating lipid peroxidation in the membranes of microorganisms, as well as those of human liver cells.

Colloidal silver proteins with low silver contents (1-6 ppm ~5-30 µg per dose) are being sold in the United States as “health food products” (Table 1), and silver sulfadiazine is used to treat second and third-degree burns.

**Table 1**

*List of Currently Promoted Silver Products in the USA*  
(from Fung e Bowen, 1996, updated)

**Unapproved products**

<b>Market</b>	<b>Product name</b>	<b>Manufacturer</b>	<b>Ingredients</b>	<b>Promoted Uses</b>
Health	Colloidal Silver	Various manufacturers	1-6 CSP per dose	Mineral supplement
food	Golden Silver Oxy Gold			“antibiotic”

**Prescription Only Drug Products**

Market	Product name	Manufacturer	Ingredients	Promoted Uses
Rx	Silver Nitrate	Lilly	1% silver nitrate	Prevention of gonorrheal ophthalmia neonatorum
	Silver Nitrate	Gordon Labs	10%, 25%, 50% silver nitrate	Warts/corns
	Silver Nitrate	Graham-Field	75% silver nitrate	Warts/corns
Rx	Silvadene	Marion Merrel Hoechst	10 mg/g sulfadiazine	silver Burn wounds
	SSD Cream	Boots	10 mg/g sulfadiazine	silver Burn wounds
	SSD AF	Boots	1% silver sulfadiazine	Burn wounds
	Thermazene	Sherwood	10 mg/g sulfadiazine	silver Burn wounds

*Information provided by the Nontraditional Drug Compliance Branch, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration and the 2000 edition of Drug Facts and Comparisons.*

*Toxicokinetics*

Following ingestion, silver is poorly absorbed from the intestine. Studies in mice, rats, monkeys, and dogs indicate that only 10% of the ingested dose is actually absorbed (Furchner *et al.*, 1968). A study by East *et al.* revealed an absorption rate in man of 18% after a single administration. In dogs exposed to inhaled silver, the highest quantities were found in the liver, with lower concentrations in the lungs, brain, and muscle tissues (Phalen and Morrow, 1973). Rodent studies have shown that hepatic deposits of silver decrease during the ten days following oral administration, while those in the spleen and brain are eliminated more slowly (Fowler and Nordberg, 1986). Excretion of silver from the body is mainly gastrointestinal (Nordberg and Gerhardsson, 1988). Regardless of the route of administration, silver is excreted in bile and, therefore, eliminated in the feces (Fowler and Nordberg, 1986). Urinary excretion (around 10 µg/day) and fecal

elimination (30-80 µg/day) has been reported from two healthy subjects (Nordberg and Gerardsson, 1988). The half-life of the metal varies with the route of administration: approximately 24 hours after oral administration (Furchner *et al.*, 1968), up to 1.7 days after inhalation (Phalen and Morrow, 1973), and as long as 2.4 days after intravenous administration (Fowler and Nordberg, 1986).

As for the nervous system, early studies indicated that silver was not capable of crossing the blood-brain barrier. However, later studies in rats demonstrated that parenteral administration of silver salts caused accumulation of the metal in neurons and glial cells of both the brain and spinal cord (Rungby and Danscher, 1983). Retrograde transport of silver by motoneurons has also been observed, although the axonal transport mechanism is still unclear (Danscher, 1982).

### *Toxicity*

Silver has toxic effects on a number of organs and tissues. Animal studies have shown that the main toxic effects of this metal are seen in the cardiovascular system, the liver, and the hematopoietic system. Left ventricular hypertrophy has been observed in turkeys maintained for 18 weeks on a diet containing 900 mg/kg of silver nitrate (Peterson *et al.*, 1973; Jensen *et al.*, 1974). Vitamin-deficient rats exposed to silver developed centrilobular hepatic necrosis with ultrastructural changes in the mitochondria and lysosomes (Grasso *et al.*, 1970). Silver can also depress upper brain functions. Mice that received parenteral silver were found to be hypoactive compared to untreated controls (Rungby and Danscher, 1984). Rungby (1990) reported that silver can reduce the total volume of pyramidal cells in the hippocampus in fetal rats. Chronic dietary exposure of animals to high doses of silver (many hundreds of milligrams / kg of body weight) leads to hyperchromatic microcytic anemia (Peterson *et al.*, 1973; Jensen *et al.*, 1974). Granules of metallic silver are deposited in the glomerulus and renal tubules of rats exposed for 10-50 weeks to drinking water containing 0.2% silver nitrate (Fuchs and Franz, 1971). Silver is also toxic to the immune system: mice given silver nitrate 0.05% for 5 weeks developed antinuclear antifibrillar autoantibodies with signs of T and B lymphocytotoxicity (Hollinger, 1996). In addition, topical application of silver sulfadiazine to burn lesions in mice caused a drastic reduction in the number of circulating granulocytes (Gamelli *et al.*, 1983).

In man, the toxic effects of silver can be divided into acute and chronic effects. Therapeutic IV administration of 50 mg or more is lethal, provoking pulmonary edema, hemorrhage, and necrosis of the bone marrow, liver, and kidneys (Fowler and Nordberg, 1986). Repeated exposure to silver salts or colloidal silver causes argyria, a deep blue-gray discoloration of the skin (particularly evident in sun-exposed areas) and gums caused by deposits of silver sulfate or metallic silver (Greene and Su, 1987; US Department of Health and Human Services, 1990.). Apart from the direct effects of these deposits, the discoloration is also due to silver-induced stimulation of the melanocytes leading to an increased production of melanin (Fung and Bowen, 1996).

Argyria also involves the tissues of the eyes (cornea and anterior lens capsule), the respiratory system, the liver, and the kidneys (Fowler and Nordberg, 1986). Silver deposits can also result in neurologic deficits. Westhofen and Schafer (1986) reported the case of a 55-year-old woman who developed progressive hypogeusia, hyposmia, vertigo, cutaneous hypoesthesia, and weakness after 9 years of self-administered silver salts to treat oral mycosis. Subsequent examinations of this patient revealed silver sulfate deposits in the perineuria of peripheral nerves, as well as in the basal membranes, macrophages, elastic fibers, and muscle fibers. Topical application of silver in man also causes immune system changes with leukopenia secondary to bone-marrow depression (Caffee and Bingham, 1982).

Treatment with silver-chelating agents such as dimercaprol (BAL) or penicillamine have proved to be ineffective in cases of silver toxicity (Jurecka, 1986; Hall and Robertson, 1990). In rare cases, circumscribed remission of cutaneous argyria has been observed after intradermal administration of 6% sodium thiosulfate or 1% potassium ferrocyanide (Goodman and Gilman, 1975). At present there is no evidence that silver is either mutagenic or carcinogenic.

### *Reproductive toxicity*

Studies in rats have also demonstrated embryotoxic effects. Shavlovski et al. (1995) maintained pregnant rats on a diet that included 50 mg of silver chloride a day. When the rats received the dietary silver during days 7-15 of pregnancy (i.e., the period of embryonic organ formation), no toxic effects were observed in the embryos. When it was administered throughout the pregnancy (days 1-20), however, there was a striking rise in the rate of embryo death, visible signs of abnormal organogenesis, including omphalocele and reductions in the size of the tails, and the ratlings that were born died within 24 hours of birth. The investigators also found a significant reduction in the copper content of both the placenta and embryonic tissues.

Intrauterine administration of 7 g of silver nitrate is fatal in humans / to human fetuses (Reinhart *et al.*, 1971).

### *Molecular toxicology*

Antioxidant deficiencies (e.g., vitamin E, selenium) appear to enhance silver toxicity. Some investigators have hypothesized that this effect is related to silver's ability to reduce the intracellular content of selenium, with consequent inhibition of glutathione peroxidase synthesis, which is selenium-dependent (Bunyan et al, 1968; Wagner *et al.*, 1975). As a corollary to their hypothesis, Bunyan et al (1975) also demonstrated that supplemental vitamin E and selenium in the diets of rats and chickens increases the animals' tolerance of even high doses of silver. Silver also decreases the activity of superoxide dismutase (an effect that might explain the



metal's embryotoxicity) (Shavlovski *et al.*, 1995) and alcohol dehydrogenase (Petering, 1976).

### **Opinion**

According to Annex IV of Directive 94/36, Silver (E. 174) can be used *quantum satis* to color both food and beverages, and the metal can also be ingested in the form of dietary supplements sold in "health-food" shops. The presence of silver (E. 174) as a coloring agent in medicinal products (which are often used for relatively short periods) may in itself represent an acceptable level of exposure. However, considering the amount of silver that can also be ingested with food (which is extremely difficult to predict) and the low reference dose recommended for humans, the Committee feels that the use of silver as colorant should be banned in medicinal products.

A recent EFPIA communication (Feb 17, 1999; March 10, 1999) affirms that silver is no longer used as colorant in medicinal products. The results of EMEA inquiries (June 16, 1998) reflected the total quantity of all colouring matters used in pharmaceutical products, including those used for packaging (e.g. blisters). The problem therefore seems to have been resolved for silver.

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