

from the introduction of aluminum directly into the blood stream via high-aluminum dialysate or the consumption of large oral doses of aluminum-containing phosphate binders. Reduced urine production (the major route for aluminum excretion) contributes to this problem. The authors noted that, in the early 1980's, reports began to appear describing aluminum neurotoxicity and osteotoxicity in children with renal failure who were not on dialysis treatment.

The agency is concerned that people with renal dysfunction may not be aware that the daily use of antiperspirant drug products containing aluminum may put them at a higher risk because of exposure to aluminum in the product. The agency considers it prudent to alert these people to consult a doctor before using or continuing to use these products on a regular basis and is including a warning in the final monograph: "Ask a doctor before use if you have kidney disease."

Flaten et al. (Ref. 49) mentioned several reports of aluminum accumulation and toxicity in individuals without chronic renal failure, especially preterm infants (primarily fed intravenously), and stated that preterm infants are at risk for aluminum loading because of their immature kidney function. Term infants with normal renal function may also be at risk because of their rapidly growing and immature brain and skeleton, and an immature blood-brain barrier. Until they are 1 to 2 years old, infants have lower glomerular filtration rates than adults, which affects their kidney function. The agency is concerned that young children and children with immature renal function are at a higher risk resulting from any exposure to aluminum. Accordingly, the agency is requiring both general warnings in § 330.1(g) on all aluminum-containing antiperspirant drug products to inform parents and others to keep these products away from children, and to seek professional assistance if accidental ingestion occurs. (See also section II.B, comment 7 of this document.)

(Comment 24) One comment submitted a research paper (Ref. 50) containing the author's theories concerning how antiperspirants and aluminum in these products may be associated with breast cancer: The secretions of the apocrine sweat glands contain androgens, which are blocked

by the antiperspirant and thus caused to spread internally. These androgens may be converted in the surrounding adipose tissues to estrogens, and excess estrogens have been associated with an increase in breast cancer. Alternatively, these excess androgens may interfere with the normal functioning of the hypothalamic-pituitary axis, thereby causing an imbalance of estrogen in the body. About 50 percent of breast cancers occur in the upper outer quadrant of the breast, and axillary sweat glands are anatomically very close to this site. A protein marker called GCDFP-15 (Gross Cystic Disease Fluid Protein), which is normally found only in the sweat glands, was found in the fluids of many breast cysts. The author postulated that the blocked axillary sweat glands would cause GCDFP-15 and other markers to migrate to the breast due to its proximity and gravity, and because the fetal precursors for apocrine sweat glands and mammary glands are the same, these migrated protein markers may stimulate the breast and play a role in the carcinogenic process.

The author also postulated that aluminum may play a role in the development of breast cancer because calcification of breast tissues (commonly seen in breast cancer) may be caused by a local electrolyte imbalance induced by the absorbed aluminum. The author noted that breast cancer in Japan was more than five times lower than in the United States and postulated this has occurred because Japanese women, especially the older population, do not use antiperspirants. The author noted that the breast cancer rate is currently on the rise in Japan, especially among young premenopausal women, and postulated that this is occurring because the young Japanese generation has adopted the western habit of using antiperspirants.

The agency finds these theories lack sufficient evidence. The agency notes that the amount of androgens produced by the sweat glands is relatively insignificant compared to normal physiologic amounts produced by the adrenals and the gonads. The agency is not aware of any studies that have shown an "internal spread" of androgens or that establish that GCDFP-15 or other protein markers are carcinogenic in humans.

The agency considers the author's views about a local electrolyte imbalance by absorbed aluminum causing breast tissue calcification

inconsistent with knowledge about the calcification process. In addition, there are many benign calcifications. Finally, many proposals (e.g., diet, lifestyle changes) have been made as to why there is an increased incidence of breast cancer among Japanese women. However, there is no evidence to associate this increase with an increased use of antiperspirants. Thus, the agency concludes that there is insufficient evidence to support these theories.

(Comment 25) The agency previously assessed the carcinogenic potential of aerosolized aluminum chlorhydrate antiperspirants in comment 22 of the TFM (47 FR 36492 at 36498 and 36499). Primary lung tumors, granulomatous lesions, and macrophagic activity were evaluated in animal studies. No increase in lung tumors was seen in the low- and mid-dose rats given doses at least 100 times greater than the expected human exposure via aerosolized antiperspirants. Normal macrophage response and pulmonary fibrosis were observed at higher doses with chronic exposure. No increase in tumors was noted in guinea pigs or hamsters at any dose levels in the studies. While the agency removed aerosol antiperspirant products containing zirconium from the market because of granuloma formation (August 16, 1977, 42 FR 41374), the agency is not aware of data that indicate aluminum antiperspirants cause foreign body granulomas or pulmonary tumors.

III. Agency Changes

1. It has been agency policy since April 3, 1989 (54 FR 13480 at 13486), that before any ingredient is included in a final OTC drug monograph, it must have a compendial (USP-NF) monograph. Compendial monographs include an ingredient's official name, chemical formula, and analytical chemical tests to confirm the quality and purity of the ingredient. These monographs establish public standards for the strength, quality, purity, and packaging of ingredients and drug products available in the United States. Eighteen of the 19 antiperspirant active ingredients that the agency proposed in § 350.10 of the antiperspirant TFM (47 FR 36492 at 36504) currently have compendial monographs. Nine of the official compendial names are the same as those proposed in § 350.10, while 10 of the names have changed slightly. (See Table 1 of this document for the previous and current ingredient names.)