Research Center Mineral Prod. Res. Lab.

Coffeyville December 22, 1961

G. F. Wyman Non-Toxicity of Lithopone

Attached is a brief report on the physiological harmlessness of lithopone which we have put together using Chemical Abstracts and other reference works here in the Research Center, including the book, "Zinc — The Metal, Its Alloys and Compounds". We have also asked the librarian at Crerar for materials, including photostats of several pertinent articles. However, pending the arrival of these, we have drawn a few conclusions, based on the abstracts of these articles which we have read.

I believe the customer is quite safe.

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Truman Kirkpatrick

Mineral Products Research Laboratory

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NONTOXICITY OF LITHOPONE AND ZINC SULFIDE

Truman Kirkpatrick

December 22, 1961

SUMMARY

Available evidence indicates that lithopone is physiologically harmless.

SCOPE OF THIS REPORT

An inquiry has been made regarding the safety of employing lithopone as an ingredient in plastics used for dishes and tableware. It is possible with this use that traces of lithopone would come into contact with food, and it is possible, although highly unlikely, that traces might actually enter food. Hence, there is a need for information as to whether lithopone is toxic and as to whether it is carcinogenic.

No experimental work was done for this report, but information available in Chemical Abstracts and in available reference books was collected and summarized. In some cases publications containing possibly relevant information were not available and photostats were requested. A supplementary report will be issued when this additional material is received. For reasons given below, however, the supplementary information is not likely to chage the picture.

Few reports are available on results of testing lithopone as such. However, since lithopone is a mixture of high purity barium sulfate and zinc sulfide, it is helpful to examine the evidence on the nontoxic characteristics of each of these two chemical substances seperately. Since both are quite insoluble and do not react with each other, there can be little doubt that lithopone is no more toxic than its two ingredients.

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NONTOXICITY OF ZINC SULFIDE AND LITHOPONE

Only a few experiments have been reported in which a direct attempt was made to determine the toxicity of zinc sulfide.

In 1950, J. L. Gabby (1) of the Glidden Company reported feeding mixtures of zinc sulfide, cadmium sulfide, and barium sulfate to rats in order to evaluate pigments used in compounding paint and blackboard crayons. He reported that no demonstrable pathologic changes occur.

F. Hahn and R. Schunk (2) reported in 1955 that they fed both ZnS and lithopone to rats at the rate of 12 to 40 grams per kilogram of body weight without harm. They are able to feed rabbits 3 grams per kilogram without difficulty, but the rabbits did not tolerate 6 grams. (3 grams per kilogram, the safe rate in rabbits, corresponds to a dose of one-half pound in an average-sized man. 40 grams per kilogram would be a dose of six pounds for a human being.)

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(1) Gabby, J. L., Toxicity of Cadmium Sulfide and Cadmium Sulfoselenide Pigments, Arch. Ind. Hyg. Occupational Med. 1, 677-84 (1950), CA 44, 8516e

(2) Hahn, F. and Schunk R. [illegible] Arch. [illegible] Pathol. Pharmakol. 226, 424-34 (1955), CA 50, 12061

NONTOXICITY OF BARIUM SULFATE

Barium sulfate is sufficiently inert and unreactive to pass through the digestive tract of man without absorption. Consequently, it has been used for many years in X-ray diagnosis of the human digestive tract by feeding the patient a "barium meal" consisting of a water slurry of barium sulfate to render the tract visible. In recognition of this and other facts, the Food and Drug Administration has authorised the use of barium sulfate as an ingredient in food additives resulting from contact with containers or equipment and food additives otherwise affecting food. (3)

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(3) Federal Register, Tuesday, August 8, 1961, pp. 7089

NONTOXICITY OF ZINC COMPOUNDS

A. Zinc Required by Normal Organisms

A good review of the biological significance of zinc has been prepared by B. L. Vallee.(4) There is evidence that zinc compounds, as such, are neither toxic nor carcinogenic to human beings or animals.

The best evidence is this: As recently shown, zinc is an essential trace element required in small amounts for normal physiological and metabolic processes in man, animals and plants. (4)

The first concrete explanation of its mode of action was given in 1940 when Keilin and Mann (5) showed that the enzyme carbonic anhydrase contains 0.33% zinc as an essential part of its molecule and, thus, that zinc is required in the elimination of carbon dioxide from the body.

The usual human intake of zinc is 10 to 15 milligrams per day. The zinc content of human organs varies from 10 to 200 micrograms per gram of wet tissue. Apparently no tissue stores zinc preferentially. The total amount of zinc in the human body has been estimated to be two grams on the average. Human whole blood contains about 900 micrograms of zinc per 100 milliliters. (4) If animals are fed a diet containing no zinc, a zinc deficiency disease develops. A similar disease has been observed in plants.

Zinc is continuously eliminated from the human body at the rate of about 10 milligrams per day in feces and about 0.4 milligrams in urine.

In a letter dated March 18, 1960, from G. F. A. Stutz, Manager, Pigment Division, New Jersey Zinc Company, to R. A. Moore of Sherwin-Williams, a statement is quoted from Dr. A. J. Lehman, Chief, Division of Pharmacology, Food and Drug Administration, to the effect that inorganic salts of zinc are acceptable in food packaging if the [illegible] of the material contributes less than 50 parts per million to the food.

Vallee, B. L., [illegible] Significance of Zinc, pp. 669-679, Zinc-The Metal, Its Alloys and Compounds, C. H. Mathewson, Editor, ACS Monograph No. 142, Reinhold Publishing Company, 1959.

(5) Keilin D., and Mann, T., "Carbonic Anhydrase: Purification and Nature of Enzyme", Biochem. J., 34, 1163-1176 (1940)

B. Cases of Zinc Poisoning

The above section indicates that very small amounts of zinc compounds are harmless and non-carcinogenic. Larger amounts may cause difficulty. Several cases of zinc poisoning have been reported. These fall into three categories: the ingestion of large amounts of zinc compounds with food or drink; direct contact with zinc or zinc salts; the inhalation of high concentrations of freshly formed zinc oxide fumes.

If a considerable quantity of a soluble zinc salt is ingested, the result is an acute and transitory illness with nausea and vomiting, diarrhea, etc. A typical circumstance producing this kind of illness is the drinking of large quantities of lemonade or other acid fruit juice which has been prepared in a galvanized bucket or container. The illness is usually short-lived. (6)

In general, zinc and zinc salts are well tolerated by the human skin. Zinc oxide for many years has been a constituent of "adhesive tape" and surgical bandages. Zinc oxide ointment has been prescribed for many skin conditions while calamine lotion (mainly zinc oxide) is a standard treatment for such skin inflammations as that resulting from poison ivy. (7) There have been reports of dermatitis due to contact with zinc salts but this seems to be a very rare occurence. (4). A contact dermatitis attributable to exposure to zinc chromate has been observed and is reported to be troublesome, persistent, and relatively disfiguring. However, the chromate, and not the zinc, is presumed to the the offending agent.(8)

A severe illness has been reported in workers who have inhaled fumes of freshly prepared zinc oxide, although equally high concentrations of zinc oxide dust formed more than a few hours before exposure are reportedly without effect. (9) The condition, known in zinc smelters as "metal fume fever" or "zinc shakes" is poorly understood.

(6) Callender, G.R. and Gentzkow, C.J., "Acute Poisoning by the Zinc and Antimony Conte in Limeade Prepared in a Galvanized Iron Can," Military Surgeon, 80, 67 (1937)

(7) The Merck Manual of Diagnosis and Therapy, Published by Merck, Sharpe and Doehme Tenth Edition, 1961, pp. 1458

(8) Hall, A.F., "Occupational Contact Dermatitis Among Aircraft Workers," J. Am. Med. Assoc., 125, 179 (1944)

(9) Clinton, M., Jr. and Drinke , P., "Industrial Poisoning by Metals," Metals Handbook p. 758, American Society for Metals, Cleveland, Ohio, 1948

NONTOXICITY OF OTHER INSOLUBLE SULFIDES

If we may expect that the ingestion of small quantities of zinc sulfide will be harmless as far as the zinc content is concerned, there remains the question of whether any difficulty might be caused by the sulfide part of the molecule.

It should first be noted that zinc sulfide is exceedingly insoluble. The solubility product of zinc sulfide is given in handbooks as 1.2×10^{-23}. Some indication of the hazard from ingesting small traces of sulfides can be gained by examining the toxicity of iron sulfide, which, though relatively insoluble, has a somewhat higher solubility than zinc sulfide, ($K_{sp} = 3.7 \times 10^{-19}$). Ferrous sulfide was found to be nontoxic when given by mouth in an investigation by C. G. Santesson. (10)

EXTRACTABILITY TESTS

In evaluating plastic wrappers and containers for packaging food, one of the criteria used by the Food and Drug Administration is information on whether any material is extracted from the package into the food. To determine extractability, the package to be tested is exposed for a considerable period of time at 135°F. to the following solvents: distilled water, 3% sodium chloride solution, 3% acetic acid solution, 3% sodium bicarbonate solution, 20% sucrose solution containing 1% citric acid adjusted to pH 3.5, liquid food fat such as a vegetable oil or lard oil, and aqueous ethyl alcohol of the appropriate concentration (needed only for alcoholic beverage use).

It would seem that if the plastic dinnerware is of a quality the average customer would accept, the amount of material extracted from it by these solvents would be, in effect, zero. This should be fairly easy to demonstrate, should it become necessary, by the manufacturer.

(10) C. G. Santesson, The effect of iron and manganous sulfides, Skand. Arch. Physiol. 79, 169-92 (1938) CA 32, 9275[e]

CONCLUSION

From the above information, it would appear likely, not only that lithopone is harmless, but that it might win Government approval for the proposed uses.

FUTURE WORK

If we desire to answer the question of whether exposure to lithopone tends to produce cancer, we might well discover that the records of the Ozark Smelting and Mining Company at Coffeyville, Kansas, contain the best evidence to be found anywhere in the United States.

We might consider a study similar to what the American Smelting and Refining Company did for arsenic compounds.

Arsenic has been under suspicion as a cancer-producing substance. The American Smelting and Refining Company had a study made by Sherman S. Pinto, M. D., in which the death reports of all active employees and pensioners for the years 1946 to 1959 were collected and analyzed. The causes of death and the percentage of deaths from cancer of various types were tabulated. Rates of cancer incidence of workers in the American Smelting and Refining arsenic plant were compared with similar data for workers in other plants of the same company and it was found that there was no significant difference. Thus, arsenic apparently does not cause cancer.

It may be objected that the sample was too small. However, it is the biggest sample which could be obtained of people who had been exposed to arsenic in large quantities and over long periods.

If we wanted to do a similar study on lithopone, the evidence of the cause of death of people in our own lithopone plant in Coffeyville might be the very best information available anywhere. It would make an interesting study.

TK:jm

PRECAUTIONARY NOTE

It is well to re-emphasize that a memorandum from H. E. Spitzer on July 9, 1959, designated the director of the Analytical Research Department as the individual who "would act as advisor, consultant and coordinator of all technical phases and should approve any requests for toxicity clearance."

Thus, the correct procedure would be to clear with James McGinness of our Analytical Research Department before saying anything to anyone outside our Company regarding the toxicity or harmlessness of any product, regardless of the material contained in this report.