

UNIVERSITY OF CINCINNATI

COLLEGE OF MEDICINE

DEPARTMENT OF ENVIRONMENTAL HEALTH

RESEARCH LABORATORY
1801 AND 1803A AVENUES
CINCINNATI, OHIO 45219

January 30, 1967

Mr. W. E. McCormick, Manager
Department of Industrial Hygiene
and Toxicology
B. F. Goodrich Company
500 South Main Street
Akron, Ohio 44318

Dear Bill:

We have completed the proposed experiments on the PVC problem, in which we measured the Ca^{45} uptake of rats that had been exposed either to Geon slurries or to vinyl chloride. I consider the findings to be positive. The second study, involving the histology of rabbits that were exposed to vinyl chloride, gave essentially negative results. I am enclosing four copies of an interim, informal report on these experiments. As soon as you have had an opportunity to assess these, perhaps we can discuss extension of the work.

It looks promising that we could use the Ca^{45} technique to screen for the specific agent. Also, we suggest that we get underway with long range exposures on a colony of 20 to 50 rats to the slurry, to be followed by X-ray and by serial kills following the injection of Ca^{45} . Something on the order of \$20,000. should see us through 6 months of experiments, in both of these areas, depending upon how ambitious the program.

Very truly yours,



Russell Tye
Associate Professor
of Environmental Health

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Encl.

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INTERIM REPORT
GOODRICH CORPORATION
OCCUPATIONAL ACROOSTEOLYSIS

by

Russell Tye
Associate Professor
Environmental Health

January 30, 1967

DEPARTMENT OF ENVIRONMENTAL HEALTH
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Introduction

The occurrence of acroosteolysis in workers involved in the production of polyvinyl chloride has proved to be quite baffling in its etiology. Consequently, two sets of experiments, in which laboratory animals were exposed to possible causative agents, have been performed. These experiments were exploratory in nature, it being hoped that one of the methods and materials used would produce information that would warrant a more thorough investigation. A set that involved the administration of radioactive calcium (Ca^{45}) to rats appears promising.

Method, 1

In that set of experiments groups of young adult male rats (Sprague Dawley, Holtzman derived, 18 weeks at death) and of immature males (same source, 10 weeks at death), were exposed to aqueous slurries, representative of the ordinary reaction product as pumped from the reactor. These slurries were obtained fresh daily and kept frozen until used. Rats were exposed to the mixture by causing them to walk or stand about in the material for periods of five hours each, five days per week, for three weeks. An additional group of young adults and another of immature adults were placed in a chamber in which vinyl chloride was maintained at a concentration of 5,000 ppm, 5 hours per day, 5 days per week, for 4 weeks.

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On the day following the final exposure, either to vinyl chloride or to the Geon slurry, each rat was injected with 0.5 ml. of Ca^{45} chloride in isotonic saline, in the tail vein. The young adults were killed 60 minutes after the injection and the immature adults, 50 minutes, by intraperitoneal injection with Nembutal.

The toes of the front feet of each rat were removed and, before the heart had ceased beating, one ml. of blood was drawn from the heart. The soft tissues were removed from the toes by digestion with aqueous sodium hydroxide. The bones were dried and weighed, then dissolved in concentrated HCl. These solutions and the specimens of blood were analyzed for radioactive Ca^{45} by methods, which we have published (1).

RESULTS

Less Ca^{45} was found in the bones of the young adult rats that had been exposed to the slurry of Geon 103EP-F7 than in the bones of controls (see table). Young adults that had been exposed to vinyl chloride (ambient vapor) or to Geon 222 showed less difference from the controls in this respect. At this point of the investigations it is a matter of opinion, but the CPM of the entire sample are believed to be more meaningful than the CPM per gram of bone, though either set of data conveys the same result.

(1) Tye, R. and Engel, J.D., Anal. Chem. 37:1225 (1965).

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The Concentration of ^{45}Ca in Tissues Following Intravenous Injection into Male Rats
That Had Been Exposed to Either Vinyl Chloride or to PVC Reaction Mixtures

Age rat, exposure	Rat no.	Wt. rat (g.)	Wt. bone (mg.)	CPM bone(1)	CPM/g bone	Wt. bone(2) (mg.)	CPM bone(2)	CPM/g bone	CPM/g blood
young adult, Geon	1	347	42	1950	45500	46	2000	43400	4170
	2	233	36	2540	70600	45	2780	62400	4560
103EP-F7, feet	3	345	42	2040	48700	44	2040	46800	4720
	4	347	36	2160	61800	47	2250	47600	4360
young adult, control	5	338	43	2590	60500	47	2060	44600	4280
	6	304	39	2750	70600	43	2880	67900	4640
	7	346	40	2420	60300	47	2410	51500	4810
	8	323	52	2990	57700	--(3)	--	--	4300
young adult, vinyl chloride, ambient	9	332	39	2650	67800	--	--	--	4020
	10	317	49	2590	52700	--	--	--	4020
	11	342	40	2330	58300	--	--	--	4210
	12	362	44	2190	49400	--	--	--	4040
young adult, Geon 222 feet	13	347	42	2660	63500	--	--	--	4470
	14	327	37	2810	75200	--	--	--	3970
immature, Geon	15	219	29	3330	114000	--	--	--	4650
	16	149	27	3920	146000	--	--	--	4720
103EP-F7, feet	17	187	25	3000	120000	--	--	--	3640
	18	227	27	2910	106000	--	--	--	5700
immature, control	19	194	30	3260	109000	--	--	--	4630
	20	214	25	2310	94000	--	--	--	4780
immature, vinyl chloride ambient	21	311	35	2990	85500	--	--	--	3220
	22	228	31	3060	99700	--	--	--	3910
	23	185	29	3960	137000	--	--	--	4820
	24	216	29	3460	119000	--	--	--	3920

{1} Toes of front feet. CPM (activity) of entire sample.

{2} Toes of rear feet, samples from frozen carcass.

{3} his animal run at different time and day in next month

A further check on the validity of the observed relationships, with respect to Ca^{45} in bone, was made with bones from the hind feet. A difference between the rats that were exposed to Geon 103EP-F7 and the controls was less evident, but still existent.

The radioactivity of the samples of bone from the immature rats showed no clear differences between groups. On average, these groups showed greater variability and higher levels than did the young adults.

The radioactivities of the samples of blood showed no patterns that were readily relatable to the levels in the bones. The concentrations of Ca^{45} in the blood of both young adult and immature rats that had been exposed to vinyl chloride were lower than in the respective controls. This was not true of the rats exposed to the slurries of Geon. Experimental investigation, with Ca^{45} , of the relationship of group to group and of blood to bone, as a function of time is in order.

In summary, it appears that measurable differences in the dynamics of calcium metabolism can be demonstrated in rats that have been exposed to Geon 103EP-F7, and perhaps to vinyl chloride, in comparison with control animals. This information encourages an expectation of successful applicability of related experimental procedures to identification of the specific causative agent of the observed acroosteolysis and to some definition of the etiology.

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Method 2

Six young adult rabbits (New Zealand white) were placed in a chamber in which vinyl chloride was maintained at a concentration of 5,000 ppm, 5 hours per day, 5 days per week. One rabbit each was killed at the ends of the first, second and third weeks. The remaining three rabbits and two controls were killed at the end of the fourth week. All animals were autopsied, and tissues were prepared for histological examination. The findings with respect to all of the exposed rabbits, and two controls are given in the pathologists report (attached, as Results, 2).

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Results, 2

An autopsy was performed on six rabbits exposed to vinyl chloride, and two controls. Tissues for microscopic examination were taken from the internal viscera and additionally from skin and bone. The skin was selected from the back of the animal, the abdomen, the ear, the feet and the front legs. Segments of bone were examined from the junction of sternum and ribs, the tail and the small bones of all feet. Special stains were prepared on the skin and bones, including Masson Trichrome, elastic fibers, PAS and PVP.

The gross examination of the rabbits revealed no abnormal findings. The microscopic examination showed no significant differences between the control animals and the animals that had been exposed, except for the lung. There was hyperplasia of the bronchial epithelium and cellular infiltration in the subepithelial tissue. The severity of the bronchitis was related to the length of exposure. It did not exceed a moderate degree in any instance.

Since special emphasis was placed on the bone and skin it should be stated that no alterations occurred in these tissues attributable to the exposure.

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