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# INHALATION TOXICITY OF ZIRCONIUM COMPOUNDS

## I. SHORT-TERM STUDIES

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THE UNIVERSITY OF ROCHESTER
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# INHALATION TOXICITY OF ZIRCONIUM COMPOUNDS

## Abstract

A total of 270 animals of 5 species was exposed by inhalation to compounds of zirconium for 6 hours per day, 5 days per week. One group of animals was exposed to $ZrO_2$ at an atmospheric concentration of 75 mg. $Zr/m^3$ for 30 days; another, to 11 mg. $Zr/m^3$ for 60 days. A third group was exposed to a mist of $ZrCl_4$ at a level of 6 mg. $Zr/m^3$ for 60 days.

Zirconium oxide produced no significant changes in mortality, growth rate, blood nonprotein nitrogen or fibrinogen, urinary protein, hematological values or histological structure. Zirconium tetrachloride at 6 mg. $Zr/m^3$ gave questionable changes in blood hemoglobin concentration and red cell counts of dogs and a slight increase in mortality of rats and guinea pigs.

Inhaled zirconium compounds deposited primarily in the lung and pulmonary lymph node, with a fraction of a per cent in the bone and considerably less in the soft tissues.

# INHALATION TOXICITY OF ZIRCONIUM COMPOUNDS

## Introduction

In recent years the element zirconium has received wide publicity as one of the potential wonder-metals. Today, annual production has increased from pounds to tons and only metallurgical difficulties limit its more widespread use. Various compounds of zirconium, on the other hand, for many years have been essentially bulk materials in the manufacture of enamels, glazes, refractories, insulators, lakes and other chemicals.

Zirconium ($Zr^{95}$) is a radioactive product of nuclear fission and consequently, knowledge of its fate in the body has possible interest. The important property of intravenously injected zirconium to prevent deposition of certain radioelements in the skeleton (especially plutonium) has led to practical medical application in the treatment of plutonium exposures(1)(2).

Only a few studies on the toxicity of zirconium compounds have been reported; and these were mainly concerned with effects when Zr was given by routes other than inhalation, although inhalation has been used under special conditions. The metabolism and distribution of carrier-free $Zr^{89}$ and $Zr^{93}$ was studied by Hamilton(3)(4) who showed that 16 days after the parenteral administration to rats about 50% of the initially absorbed Zr was present in the bone with a half-time of excretion of about 80 days. Following

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(1) Schubert, J., "Treatment of Plutonium Poisoning by Metal Displacement," Science, 105, 389, (1947).

(2) Schubert, J., "An Experimental Study of the Effect of Zirconium and Sodium Citrate Treatment on the Metabolism of Plutonium and Radioyttrium," J. Lab. and Clin. Med., 34, 313, (1949).

(3) Hamilton, J.G., "Summary of Metabolism of Carrier-Free Fission Products in the Rat," Atomic Energy Comm., MDDC-1002, Declassified 1947.

(4) Hamilton, J.G., "Tracer Studies of Fission Product Metabolism," Atomic Energy Comm., MDDC-1062, Declassified 1947. Also reports MDDC-1001, 1143, and 1275.

intrapulmonary administration, there was a high degree of retention in the lung (90% after 16 days). Oral absorption was very low. In a later study[5] an aerosolized radioisotope of Zr was inhaled by rats; 85% to 70% of the $Zr^{95}$ deposited in the lungs was retained after 12 to 45 days.

The distribution of intravenously injected radioactive colloids of $Zr^{95}$ was confined mainly to the liver and spleen of mice, rats, and rabbits when the particle size was large; primary localization was in the bone marrow, however, when the particle size was small.[6] The bulk of the colloid tended to remain at the site of deposition at least for 22 days.

A number of studies of oral and intraperitoneal toxicity showed that zirconium is of relatively low toxicity by these routes. In a series of experiments by Cochran et al.,[7] the acute oral LD50's for rats ranged from 853 to 2290 mg Zr/kg for zirconyl acetate, chloride, nitrate, zirconium sulfate and sodium zirconyl sulfate; the acute intraperitoneal LD50's ranged from 63 to 939 mg Zr/kg. Three cc. of a 10% zirconium silicate suspension injected intraperitoneally into guinea pigs gave no toxic effects.[8] McClinton and Schubert[9] found the intraperitoneal LD50 of zirconyl chloride injected in 1 to 5 doses to be 1710 mg.Zr/kg. when the material was dissolved in trisodium citrate and 247 when dissolved in sodium gluconate.

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(5) Kawin, B., Copp, D.H. and Hamilton, J.G., "Studies of the Metabolism of Certain Fission Products and Plutonium," Atomic Energy Comm. UCRL-812, (1950)

(6) Dobson, E.L., Gofman, J.W., Jones, H.B., Kelly, L.S., and Walker, L.J., "Studies with Colloids Containing Radioisotopes of Yttrium, Zirconium, Columbium, and Lanthanum," Atomic Energy Comm. AECD-2055 Declassified (1948)

(7) Cochran, K.W., Doull, J., Mazur, M., and DuBois, K.P., "Acute Toxicity of Zirconium, Columbium, Strontium, Lanthanum, Cesium, Tantalum and Yttrium." Arch. Ind. Hyg. Occ. Med., 1, 637, (1950)

(8) Harding, H.E., "The Toxicology of Zircon." Brit. J. Ind. Med., 5, 75, (1948)

(9) McClinton, L.T. and Schubert, J., "The Toxicity of Some Zirconium and Thorium Salts in Rats." J. Pharm. and Exptl. Therp., 94, 1, (1948)

Various pharmacologic actions,[10,11,12,13] effects on nutrition,[14] and on enzymes[15] have also been reported.

In this report are given the acute effects observed in two experiments when animals inhaled the insoluble $ZrO_2$, and in one experiment with a mist of the soluble $ZrCl_4$ (or $ZrOCl_2$).

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(10) Niekerk, J. von., "Pharmacological Action of Salts of pure Zr and pure Hf." Arch. Exptl. Path. Pharmacol., 184, 686 (1937)

(11) Mezey, E. and Mezey, K., "Effect of Metal Salts on the Isolated Heart Muscle." Magyar Biol. Kutatointezet Munkai, 10, 371 (1938).

(12) Fairhall, L.T., "Inorganic Industrial Hazards." Physiol. Rev., 25, 182 (1945)

(13) Lendle, L., "Hefters Handbuch der Experimentellen Pharmakologie" (1934)

(14) Richet, C., Gardner, Goodbody, "Effects of Salts of Zirconium, Titanium, and Manganese on Nutrition." Compt. rend. 181, 1105, (1925)

(15) Gould, B.S., "Effects of Thorium, Zirconium, Titanium, Cerium on Enzyme Action." Proc. Soc. Exptl. Biol. Med. 34, 381 (1936)

## Materials and Methods

### Zirconium Compounds

Zirconium compounds of a high degree of purity were obtained from two sources for use in these studies. The major impurity was hafnium in all cases and represented 3 to 4% of the total weight except in the instance of the oxide low in Hf used in the 60-day experiment. The other major impurities as determined spectrographically are shown in Table 1.

Table 1

Percentage of Major Impurities in Zirconium Compounds

| | $ZrO_2$ (1) | $ZrO_2$ (2) | $ZrCl_4$ (3) |
|---|---|---|---|
| Al | < .001 | .026 | .005 |
| B | < .00002 | Trace | ------ |
| Ba | .0002 | .062 | Trace |
| Ca | .002 | .071 | .008 |
| Cr | .0001 | Trace | ------ |
| Cu | .0025 | .008 | Trace |
| Fe | .0025 | .049 | .004 |
| Mg | .0001 | .160 | .006 |
| Ni | .0003 | ----- | ----- |
| Pb | .0225 | ----- | ----- |
| Si | < .001 | .470 | .01 |
| Ti | .006 | .180 | .001 |
| V | .0004 | ----- | ----- |

(1) Carbide and Carbon Chemicals Division. Union Carbide and Carbon Corporation. Used in 60-day study.

(2) Titanium Alloy Manufacturing Division, National Lead Company. Used in 30-day study.

(3) Titanium Alloy Manufacturing Division, National Lead Company. Used in 60-day study.

Spectrographic analyses were furnished by the suppliers and qualitatively checked by our own laboratories.

Inhalation Exposure Unit

All experiments were carried out in a copper-lined chamber constructed of wood with observation windows on three sides. The dimensions of the chamber were 6 by 8 by 6 feet high (183 by 244 by 183 cm.) so that the volume was 288 cubic feet (8.17 cubic meters). Of the total volume approximately 2% was occupied by animals.

A centrally located duct in the ceiling of the chamber served as the inlet for diluted aerosol. Baffles below the inlet and two fans near the ceiling dispersed the aerosol and distributed the material more or less uniformly throughout the chamber. In the four bottom corners were outlets connected to an exhaust system and for the sake of safety the chamber was kept at a pressure a few hundredths of an inch of water less than atmospheric pressure. Air turnover during exposure was approximately 140 cfm, or one change every two minutes with no recycling. Although the incoming air was not conditioned in the strictest sense of the word, it was cooled and dehumidified and thus approximated an optimal environment for the test animals. Wet and dry bulb temperatures were recorded on a Foxboro recorder.

Aerosol Feed.

Two types of aerosol feeds were used during the studies, one for $ZrO_2$ dust and the other for $ZrCl_4$ mist. The $ZrO_2$ was twice ground in a Mikropulverizer to a mean bulk particle size of about 1.5$\mu$ and fed into the inlet air stream by a Wright[16] dust feed. The $ZrCl_4$ was dissolved in water to give a specific gravity of 1.020 (43.5 g/l) at 20° C. and aspirated into

(16) Wright, B.M., "A New Dust Feed Mechanism." J. Sci. Instr. 27, 12 (1950)

the inlet duct by the mist generator previously described[17]. In essence, the system consisted of an aspirator jet assembly held by a rubber stopper in a hole in the bottom of a one liter round bottom flask and so mounted that the jet was immersed in approximately 200 ml. of solution within the flask. The aspirator consisted of a stainless steel inlet tube closed at the top and having 4 holes 0.027" in diameter drilled through the tubing. These air jets forced high velocity air at right angles across 4 holes also 0.027" diameter drilled into a collar and thus produced a submerged spray of mist which was carried out of the top of the round bottom flask. A side-arm on the flask served as an inlet for liquid flowing by gravity feed while another side-arm functioned as a constant-level and run off.

Exposure Conditions

The means of the concentrations maintained for the 3 zirconium exposures are given in Table 2. In all cases, hourly samples were taken with a filter paper sampler and weighed on an analytical balance; spectrographic analysis of each day's accumulation of filter paper samples was used to verify the weight-samples and to make such slight adjustments in concentration results as might occasionally arise from varying amounts of nuisance dust.

In the case of $ZrO_2$, the factor converting weight-analysis to spectrographic analysis was close to 1.0. The $ZrCl_4$, however, upon dissolving in water was converted to $ZrOCl_2$ and the solid material collected on the filter papers had a composition of $ZrOCl_2 \cdot 8H_2O$. Thus the $ZrCl_4$ exposure is more properly an exposure to $ZrOCl_2$. Theoretically, a solution of $ZrCl_4$ should contain 2 moles of HCl per mole of $ZrOCl_2$ but most of the HCl was lost during solution and by reaction with the chamber ducts and walls. Semi-quantitative determinations of free HCl in the chamber atmosphere showed the

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(17) Laskin, S., "Dispersion of Aerosols." UR report No. 38 (1948)

TABLE 2

Summary of Exposure Conditions

| | Insoluble | | Soluble |
|---|---|---|---|
| | $ZrO_2$ | $ZrO_2$ | $ZrCl_4$* |
| Duration (calendar days) | 30 | 60 | 60 |
| (hours) | 113 | 264 | 270 |
| Concentration (mg. compd/$m^3$) | | | |
| Mean | 100.8 | 15.4 | 14.9* |
| S. Deviation | 6.5 | 0.7 | 1.1* |
| Number of Samples | 109 | 265 | 263 |
| Mean Concentration (mg. Zr/$m^3$) | 74.6 | 11.4 | 5.8 |
| Mass Median Particle Diameter ($\mu$) | 1.5 | 1.6 | 0.57 |
| Mean Temperature (°F.) | 74 | 75 | 72 |
| Mean Relative Humidity (%) | 47 | 60 | 53 |

* The $ZrCl_4$ was aspirated as a solution and the composition of the suspended solid was actually $ZrOCl_2 \cdot 8H_2O$, although calculated here as $ZrCl_4$.

presence of less than 10% of the expected amount or about 0.3 ppm; this is considerably below the accepted MAC of 5 ppm for HCL.

Weekly samples of chamber atmosphere taken with a modified cascade impactor and plotted on a logarithmic-probability grid[18] showed only slight variations during the experiments. The $ZrO_2$ dusts in general had mass-median diameters of 1.5$\mu$; the $ZrOCl_2$ mist was much smaller and averaged about 0.6$\mu$. Electron micrographs were taken of the smaller sizes.

Included also in Table 2 are the mean values for temperature and relative humidities for the 3 exposures. Temperatures in general were constant to within $\pm$ 3° F. of the means shown; relative humidities to within $\pm$ 6%.

Animal Species

A total of 271 animals of 5 species was exposed to Zr compounds. The higher level of $ZrO_2$ (75 mg.Zr/$m^3$) was intended primarily as an exploratory experiment and consequently only 28 animals of 3 species were used. Each of the 60-day studies included about 120 animals (Table 3).

In all experiments, exposures to zirconium compounds were for 6 hours daily, 5 days per week.

(18) Laskin, S., "Measurement of Particle Size," National Nuclear Energy Series, New your, McGraw Hill Book Company, Inc., 1949, div. 6, vol. 1, chap. 10.

TABLE 3.

Animals Exposed to Zirconium

| Compound | $ZrO_2$ | $ZrO_2$ | $ZrCl_4$ |
|---|---|---|---|
| Level | 75 mg. $Zr/m^3$ | 11 mg. $Zr/m^3$ | 6 mg. $Zr/m^3$ |
| Duration | 30 days | 60 days | 60 days |
| Species | | | |
| Cat | ---- | 4 | 4 |
| Dog | 2 | 4 (8)* | 8* |
| Guinea Pig | ---- | 20 | 20 |
| Rabbit | 6 | 19 | 20 |
| Rat | 20 | 72 | 72 |

* Four dogs exposed to $ZrCl_4$ were subsequently also exposed to $ZrO_2$.

## RESULTS

### Mortality

During the exposure of animals to $ZrO_2$ few deaths were noted at either level. Only one rabbit died during the 75 mg $Zr/m^3$ study; one rabbit and one guinea pig at the 11 mg. study (matched by deaths in the control group).

Zirconium tetrachloride was more lethal to rats and guinea pigs than was the oxide, but did not kill rabbits, cats, or dogs (Table 4). The cause of death was not well established in any case, but appeared to be an intercurrent respiratory infection. No deaths occurred during the first week, a few during the second and third, with 55% of the total taking place during the fourth week.

### Weight Response

Throughout the exposure periods of the three studies, the weekly weight responses were identical with those of normal animals. Adult cats, dogs, guinea pigs, and rabbits maintained their weights with only slight random fluctuations; both male and female rats showed small gains consistent with their ages. Even in the exposure to $ZrCl_4$ which caused mortality in guinea pigs and rats there was no pronounced effect on growth except in dying animals a few days before death.

### Hematology

Red blood cell and differential white cell counts, as well as determinations of hemoglobin, mean corpuscular cell volume and clotting time were made weekly on 3 dogs exposed to $ZrCl_4$. The hematological program started four weeks before exposure while the dogs were being conditioned in the exposure chamber and continued throughout the nine weeks that $ZrCl_4$ mist was being introduced.

All dogs showed a decrease in the amount of hemoglobin in the blood

TABLE 4.

Mortality

| Week of Exposure | $ZrO_2$ 75 mg.Zr/$m^3$ | $ZrO_2$ 11 mg.Zr/$m^3$ | $ZrCl_4$ 6 mg.Zr/$m^3$ |
|---|---|---|---|
| 1 | 1 rabbit | 1 guinea pig | 0 |
| 2 | 0 | 1 rabbit | 2 guinea pigs |
| 3 | 0 | 0 | 1 " ", 1 rat |
| 4 | 0 | 0 | 6 rats |
| 5 | 0 | 0 | 0 |
| 6 | ----- | 0 | 0 |
| 7 | ----- | 0 | 0 |
| 8 | ----- | 0 | 1 rat |
| 9 | ----- | 0 | 0 |
| Total | Rabbit 1/6* | Guinea Pig 1/20<br>Rabbit 1/20 | Guinea Pig 3/20<br>Rat 8/72 |

* The fraction represents the ratic of the number of deaths to the total number exposed.

following the start of exposure; a minimum was reached after approximately 4 weeks. The maximal decreases ranged from 1.6 to 3.4 g (average 2.5). On the other hand, the downward trend was also in evidence during the conditioning period when maximum losses of from 0.7 to 2.9 g/100ml. were seen (figure 1).

Depressions in the red cell counts were not as pronounced nor as uniform as those in hemoglobin content but were nevertheless of sufficient magnitude to be worthy of comment. The lowest depression occurred in the period of approximately 5 to 7 weeks after start of exposure but was not uniform for all 3 animals. Maximal decreases ranged from 0.5 to 1.8 million/$mm^3$ as compared with a downward trend ranging in magnitude from 0.7 to 0.9 million/$mm^3$ during the conditioning period.

No other hematologic changes of any significance were found.

Four dogs exposed to 11 mg $Zr/m^3$ as $ZrO_2$ and 2 dogs exposed at the 75 mg level of the same compound showed no hematologic changes during semi-monthly intervals of analysis.

Biochemistry

No significant blood or urine changes were found among the criteria studied. Blood nonprotein nitrogen and urinary protein concentrations were followed semi-monthly in 4 dogs and 4 rabbits exposed to $ZrCl_4$ and in the same number of animals exposed to $ZrO_2$ at a level of 11 mg.$Zr/m^3$. Blood fibrinogen levels also remained constant at the same time in 4 dogs in each of the two experiments mentioned above.

Histology

Zirconium compounds did not produce any histological changes that could be attributed to this element. Furthermore, the abnormalities that were found were similar for all species regardless of dose, duration of exposure or compound inhaled (Table 5 and 6).

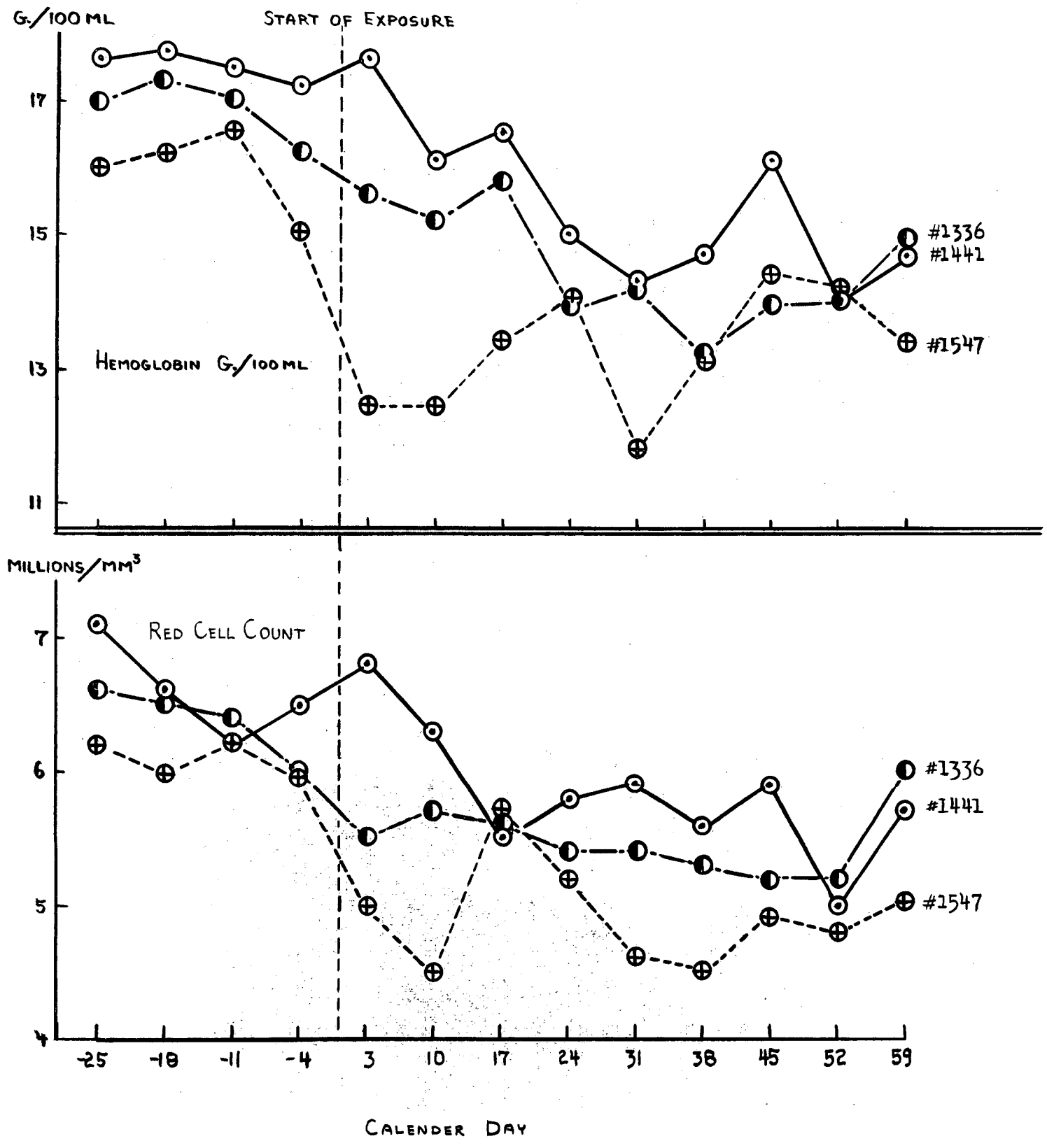


Figure 1. Hematologic Changes in Dogs During $ZrCl_4$ Exposure

TABLE 5.

Histology Following Exposure To $ZrO_2$

| Species | Ratio of Abnormal Findings | | | |
|---|---|---|---|---|
| | Lung(1) | Kidney(2) | Liver | Other |
| $ZrO_2$ (75 mg.Zr/$m^3$, 30 days) | | | | |
| Dog | 0/2 | 0/2 | 0/2 | (3) |
| Rabbit | 1/6 | 0/6 | 0/6 | 0/6 |
| Rat | 3/6 | 0/6 | 0/6 | 0/6 |
| $ZrO_2$ (11 mg.Zr/$m^3$, 60 days) | | | | |
| Cat | 3/4 | 0/4 | 0/4 | 0/4 |
| Dog | (4) | (4) | 0/4 | (4) |
| Guinea Pig | 9/18 | 0/18 | 0/18 | 0/18 |
| Rabbit | 2/10 | 1/10 | 0/10 | 0/10 |
| Rat | 8/10 | 0/10 | 0/10 | 0/10 |
| Control Animals | | | | |
| Rabbit | 5/9 | 0/9 | 2/9 | 0/9 |
| Rat | 9/10 | 0/10 | 0/10 | 0/10 |

(1) Congestion, edema, hemorrhage; occasional consolidation.
(2) Interstitial nephritis.
(3) Granulomatous lesion of pulmonary lymph node in one animal.
(4) Parasitic granulomata in lung, liver, kidney, and pulmonary lymph nodes of 3 of 4 animals.

TABLE 6.

Histology Following Exposure to $ZrCl_4$

| Species | Ratio of Abnormal Findings | | | |
|---|---|---|---|---|
| | Lung(1) | Kidney(2) | Liver | Other |
| | $ZrCl_4$ (6 mg.Zr/$m^3$, 60 days) | | | |
| Cat | 4/4 | 1/4 | 0/4 | (3) |
| Dog | 4/4 | 2/4 | 0/4 | 0/4 |
| Guinea Pig | 4/17 | 17/17 | 0/17 | 0/17 |
| Rabbit | 3/10 | 7/10 | 0/10 | 0/10 |
| Rat | 12/25 | 6/25 | 0/25 | 0/25 |
| | Control Animals | | | |
| Rabbit | 1/10(4) | 3/10 | 0/10 | 0/10 |
| Rat | 1/10(5) | 4/10 | 1/10 | 0/10 |

(1) Presence of granular material in phagocytic cells; inflammation in only one guinea pig.
(2) Interstitial nephritis.
(3) Two animals of four had some degree of testicular atrophy.
(4) Prurulent bronchitis.
(5) Prurulent pneumonia.

The lungs showed varying, but small, amounts of congestion, edema and hemorrhage, approximately half of all animals having histological lesions. Control animals, however, exhibited a similar rate of incidence. In all exposed animals, an apparently granular material, brownish-black and doubly refracting, was found in alveolar walls and in phagocytes. Occasionally, this dust was also seen in bronchi and lymph nodes.

Among the other tissues, only the kidney consistently showed damage. These renal lesions were a low-grade interstitial nephritis of parasitic origin. Occasionally, parasitic granulomata were found, and two instances of testicular atrophy were noted among 160 animals.

Zirconium Concentration in Tissues

The pattern of deposition of zirconium in tissues was quite similar in animals exposed to either $ZrO_2$ or $ZrOCl_2$. By far the largest amounts were found in the lung and in the pulmonary lymph nodes (Table 7), but with large variations among species. The rat lung retained more Zr (158 $\mu g/g$ to 361$\mu g/g$) than was found in the lungs of other species; the rabbit least (16$\mu g/g$ to 69$\mu g/g$). In general, the pulmonary lymph node concentration was about the same as that of the lung, but tended to be higher in dogs than in rats. The kidney, liver, and femur each contained only a few tenths of a per cent of the lung concentration (Table 8).

Analysis of samples taken in a serial sacrifice schedule of rats exposed for 60 days to $ZrOCl_2$ (6 mg.Zr/$m^3$) showed that the inhaled material was rapidly deposited in the lung and retained for a considerable period of time (Table 9). The data were too scattered, however, to allow curves of deposition and retention to be calculated. Qualitatively, the Zr removed from the lung appeared to accumulate in the pulmonary lymph node with only small amounts going to the femur and liver.

TABLE 7.

Mean Zirconium Concentration in Tissues

| Species | Number of Animals | Lung ($\mu g/g$) | Pulmonary Lymph Node ($\mu g/g$) |
|---|---|---|---|
| $ZrO_2$ - 75 mg.Zr/$m^3$ -30 Days | | | |
| Rat | 10 | 220 | 21 |
| Dog | 2 | 129 | 362 |
| Rabbit | 6 | 24 | |
| $ZrO_2$ - 11 mg.Zr/$m^3$ - 60 Days | | | |
| Rat | 10 | 158 | 17 |
| Dog | 4 | 74 | 731 |
| Rabbit | 10 | 16 | |
| Cat | 4 | 20 | |
| Guinea Pig | 18 | 71 | |
| $ZrOCl_2$ - 6 mg.Zr/$m^3$ - 60 Days | | | |
| Rat | 10 | 361 | 55 |
| Dog | 4 | 87 | 360 |
| Rabbit | 10 | 69 | |
| Cat | 4 | 101 | 270 |
| Guinea Pig | 17 | 201 | |

TABLE 8.

Mean Zirconium Concentration ($\mu g/g$) in Tissues of Animals Exposed to $ZrOCl_2$*

| Tissue | | Rat | Dog | Rabbit | Cat | Guinea Pig |
|---|---|---|---|---|---|---|
| Lung | Conc. | 361 | 87 | 69 | 101 | 201 |
| | No. | (10) | (4) | (10) | (4) | (17) |
| Pulmonary Lymph Node | Conc. | 55 | 360 | ----- | 269 | ----- |
| | No. | (7) | (4) | ----- | (4) | ----- |
| Kidney | Conc. | 1.17 | 0.40 | 0.14 | 0.15 | 0.68 |
| | No. | (10) | (4) | (10) | (4) | (17) |
| Liver | Conc. | 0.19 | 0.35 | 0.04 | 0.28 | 0.07 |
| | No. | (10) | (4) | (10) | (4) | (17) |
| Femur | Conc. | 1.00 | 0.40 | ----- | 0.49 | ----- |
| | No. | (9) | (4) | ----- | (3) | ----- |

* Animals were exposed during 60 calendar days (270 hours) to 6 mg $Zr/m^3$.

TABLE 9.

Deposition and Retention of Zirconium in Rat Tissues
($\mu$g Zr/g)

| Week of Exposure* | No. of Rats | Lung | Pulmonary Lymph Node | Femur | Liver |
|---|---|---|---|---|---|
| 2 | 3 | 81 | --- | 0.41 | 0.07 |
| 3 | 3 | 54 | --- | 0.43 | 0.16 |
| 4 | 3 | 119 | --- | 1.19 | 0.20 |
| 6 | 3 | 180 | --- | 0.82 | 0.39 |
| 9 | 10 | 361 | 55 | 1.00 | 0.19 |
| **Weeks Post Exposure** | | | | | |
| 4 | 2 | 254 | 79 | 1.35 | 0.18 |
| 6 | 2 | 538 | 112 | 0.97 | 0.13 |
| 8 | 2 | 254 | --- | 1.67 | 0.15 |
| 24 | 2 | 346 | 422 | 0.74 | 0.09 |

* Animals were exposed during 60 calendar days (270 hours) to $ZrOCl_2$ (6 mg $Zr/m^3$) and subsequently maintained on stock diet with no further exposure.

## DISCUSSION

Under the conditions of this experiment, both $ZrO_2$ amd $ZrOCl_2$ must be regarded as relatively harmless materials. Exposure of animals to a high concentration of a mist of $ZrCl_4$ ($ZrOCl_2$), however, gave an increase in the mortality rate perhaps because free HCl is present. On the other hand, the slight toxicity is probably not due to the toxicity of HCl *per se* because the amounts found in the chamber were well below (1/10 to 1/3) the MAC value.

In the experiments performed to date, the physiological inertness of zirconium compounds was not altered by the 3 to 4% of hafnium ordinarily present but not in the $ZrO_2$ used in the 60-day experiment. No information is available on the chemical toxicity of hafnium compounds.

The deposition of $ZrO_2$ in the lung is typical of insoluble material, but the amount of Zr deposited from the water-soluble $ZrOCl_2$ is equally large and shows a similar distribution in the remaining tissues. Presumably, the oxychloride is converted to hydroxide at physiological pH and is therefore retained to a large extent in the lung despite the relatively small particle size when inhaled. The experiments reported here are not sufficiently definitive to establish a biological retention time for zirconium compounds, but it is apparent that zirconium leaves the lung only very slowly.

## SUMMARY

1. Inhalation of $ZrO_2$ in concentrations of 75 mg.Zr/$m^3$ for 30 days, or 11 mg.Zr/$m^3$ for 60 days produced no significant changes in animals in mortality rate, growth, biochemical criteria, hematological values, or histopathological structure.

2. Inhaling an atmospheric concentration of 6 mg.Zr/$m^3$ in the form of a mist of $ZrCl_4$ for 60 days gave decreases of borderline significance in hemoglobin and red cell count of dogs and a small increase in mortality in rats and guinea pigs. All other criteria were normal.

3. Zirconium compounds were deposited and retained primarily in the lung, with concentrations in the pulmonary lymph node of the same order of magnitude. The relative amounts of Zr in the bone were low, and in soft tissues almost negligible.

## Acknowledgements

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