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BOX No. 4NN-326-87-8 30 of 45

FOLDER YTTRIUM - Production July 1, 1957 - June 30, 1958

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By JWN Date 9/9/71

SUBJECT: YTTRIUM - PRODUCTION

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SPECIAL REREVIEW
FINAL DETERMINATION
UNCLASSIFIED
By: R Anderson
Date: 8-14-86

DATE: JULY 1, 1957 - JUNE 30, 1958

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RETURN TO: Special Materials Branch
Lockland Area Office

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AEC-CH FORM 146 (11/15/48)

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GENERAL ELECTRIC [redacted]
COMPANY

AIRCRAFT NUCLEAR PROPULSION DEPARTMENT

TELEPHONE VALLEY 1-7400 . . . . CINCINNATI 15, OHIO

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November 18, 1957

Lt. Col. L. Standifer, Chief
Lockland Area Office
US Atomic Energy Commission
Cincinnati 15, Ohio

SUBJECT: **THE NEED FOR INFORMATION CONCERNING THE TOXICITY OF RADEX AND RARE EARTH COMPOUNDS**

Dear Lt. Col. Standifer:

TECHNICAL BR.-LAO	
CHIEF	
RWB	
GK	
JFW	
RAR	
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JDS	
RER	
TASK FILE	
T. BR. FILE	
CEN. FILE	
SUSPENSE	

There is a vital need for definite information on the toxicity of stable radex and rare earth compounds. This is particularly true concerning inhalation and sensitivity studies. This conclusion resulted when a lengthy literature search revealed that no research had been performed for inhalation studies with these materials to determine the toxic response. Also, personal contacts were made with acknowledged toxicologists with the same conclusion.

It is the purpose of the ANP Department's Industrial Hygiene Unit to present this problem to the AEC to stress that a true need exists for this information and request that a research program be initiated in the near future.

The following reasons are listed in order to accent this need for such action.

1. Until the last few years, the cost for these materials was prohibitive and industrial applications were a rarity; however, recent processing advancements and their very desirable nuclear properties have skyrocketed the amount of material reaching the market, primarily for the nuclear industry.

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2. Until now, this Department has been processing these materials in gram and pound lots. Within the next year, the following are the amounts to be processed.

   a. Radex--10 to 20 tons per year.

   b. Various rare earth materials such as gadolinium and lutecium--one ton per year.

   c. Metals, oxides, halides, and hydrides will be processed in both the powder and solid states.

3. A possible legal problem arises by the fact that certain phases of the process are subcontracted to outside companies. They in turn request information from the General Electric Company on the toxicity and hazards when handling the materials.

4. Considering the desirable properties of these materials, it is obvious that the yearly consumption will increase.

5. The use of these materials undoubtedly is not restricted to this installation and should be considered on a national basis.

6. A lack of such information tends to produce delays in production scheduling.

7. Personnel are reluctant to handle materials when the hazardous properties are unknown.

8. The entire nuclear industry would benefit from such a program.

For the above-listed reasons, it is requested that the Atomic Energy Commission designate a research grant to determine the actual hazards involved.

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A report by Dr. H. E. Stokinger, chief, toxicologic services, USPHS, accompanies this letter. The title is, "Background Toxicologic Information and a Suggested Program of Toxicologic Research on the Lanthanons (Rare Earths)."

Very truly yours,

P. C. Adams

P. C. Adams, Industrial Hygienist

PCA:DM

Enc.

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NEED FOR TOXICOLOGIC RESEARCH ON THE LANTHANONS
(Rare Earths)

BACKGROUND TOXICOLOGIC INFORMATION - LITERATURE SURVEY

There has been a phenomenal change in outlook in the very recent past on the industrial applications of the lanthanons. This situation has arisen as a result of the introduction of ion exchange methods which permit quantitative separation of the difficultly separable lanthanons. The methods have now been brought to a stage where the amounts available are currently in the order of 100-pound lots, with tonnage quantities available in prospect.

Associated with the industrial applications of the lanthanons will be the usual health hazards from exposure by inhalation, skin and eye. Already limited toxicologic information indicates a high degree of toxicity for the lanthanons if they gain access to the blood stream or upon direct contact with exposed surfaces, such as the eye or mucous membranes. Without adequate toxicologic information, the degree of control believed required for safe handling could be unnecessarily costly in plants with good industrial hygiene supervision; on the other hand, such controls, lacking among subcontractors, open the way to serious risks. Toxicologic information should be available for dissemination to subcontractors and prime contracting agencies alike.

Acute Toxicity. Unfortunately no information is available on the health hazards that may be expected from inhaling dusts of these materials or from their contact with the skin. The one study by Grant and Kern (1) on the effects of a limited number of lanthanons on the eye indicate severe effects, direct contact of the lanthanons resulting uniformly in permanent corneal opacity. The relative affinity of six lanthanons compared to calcium for the corneal stroma is far greater than any other nine monovalent or divalent elements tested. EDTA removed lanthanum from the corneal stroma, but other lanthanons were not investigated in this respect. Other aspects relating to the effects of lanthanons on the eye are discussed. There was no correlation between the order of response on the cornea found by Grant and Kern and the order of oral toxicity in mice among the lanthanons as found by Graca [5]. A closer, but more limited relation existed between the eye response and the systemic (blood) responses [6].

Some work on the acute oral and intraperitoneal toxicity of lanthanum and yttrium has been reported by Cochran, et al [2]. The intraperitoneal LD_{50} dose of lanthanum salts was far smaller than the oral LD_{50} value by a factor of from 6-20. Lanthanum was found to stimulate the activity of succinic dehydrogenase as does aluminum; both lanthanum and yttrium inhibited adenosine triphosphatase activity at $10^{-3}M$. Horecker, et al. [3] had already shown that certain rare earths and aluminum and chromium had a promoting effect on the succinic dehydrogenase-cytochrome oxidase system. The relative toxicity of lanthanum has been compared with tantalum and thorium compounds in the developing chick embryo by Machlin, et al. [4]. These studies indicate that lanthanum chloride was not highly toxic in the developing chick embryo, hemorrhage being the most prevalent symptom. A stiff hock joint syndrome was described. A comparative study of the toxicity of stable rare earth compounds has been reported by Graca [5] in which the comparative intraperitoneal toxicity of cerium, lanthanum, neodymium and praseodymium chlorides and their citrate complexes in mice and guinea pigs were made. Complexing was shown to enhance the distribution and consequently the toxicity of these compounds. The characteristic 2-stage signs of toxicity were described. Dr. Graca is continuing his studies on the acute and chronic toxicity of a number of additional rare earths, both intraperitoneally and orally.

Anticoagulant Effects. One of the most revealing findings on the toxic potentialities of the elements of the lanthanon series, Nd, in particular, is that resulting from the attempted use as a blood anticoagulant in man and in animals [6,7,8]. When attempts were made to render the blood of patients incoaguable [6], thrombophlebitis or thrombosis occurred at the site of injection, depending on the salt used. Following repeated injections of a few milligrams each, the following toxic signs and symptoms were observed: Low fever (101° F), headache, sweating, muscle and abdominal pains, nausea, vomiting, hematuria and nephrosis. The acetates of La and Ce in doses of 1.6-5 mg/kg in man produced toxic signs of more severe intensity. Nd produced hemoglobinemia in patients at doses of 1.2-1.8 mg/kg. A dose of 4-5 mg/kg body weight in man of the lanthanons was required to render the blood incoaguable; the anticoagulant effect was temporary, lasting a few hours. The action of the lanthanons is believed to be on prothrombin and perhaps on thromboplastin and thrombin [8]. Oddly, Meyer [9] concluded that cerium has no effect on the formed elements of the blood as a result of studies in animals. In connection with the pronounced effects of the lanthanons on red blood cells, it is noteworthy that the toxicity of the lanthanons has been reported to be greatly reduced by their use as nicotinates (10). The 3-sulfoisonicotinate of Nd was still highly toxic to rabbits, however, producing hematuria and severe nephrosis in two days at doses of 15 mg/day (7).

Distribution and Excretion (Stable Isotope). With the exception of a few reports (11, 12, 13) almost no work has been done on the distribution and excretion of toxicologically significant amounts of the stable rare earths; on the other hand, the distribution and excretion of the rare earths in tracer doses is very well known (Hamilton, Scott, Durbin). Hara (11) reported the distribution in the viscera of young rats of small doses (3 mg) of $NdCl_3$. Considerable amounts were found in the liver, spleen, lungs, stomach, intestines and contents, but only small amounts in the kidney, pancreas and heart. The feces contained appreciable amounts of Nd, indicating bile absorption. In a second study (12) Hara determined the distribution of $NdCl_3$ administered orally to rats at a level of 500 mg/day for five successive days. Largest amounts were found in liver and spleen. When given as the insoluble oxalate, very small amounts were found in any tissue. Intramuscular injection of $NdCl_3$ showed very little absorption from the injection site. It was concluded that Nd tends to be retained in insoluble form in the tissues of the reticuloendothelial system. MacDonald (13) showed that yttrium by repeated intraperitoneal injection in rats was not a "bone seeker" but that the contents of the tissues of the reticuloendothelial system, the liver, spleen, lung and kidney contained the bulk of the deposited yttrium.

These results clearly demonstrate the difference in distribution of an element as affected by the amount of dose; from radiotracer doses, yttrium is considered to be a "bone seeker".

The remainder of the toxicologic work on the lanthanons has been medically oriented, in that studies have been directed to finding sites of special affinity in the body for the radioisotopes of the lanthanon (14). This work has produced much useful information on the distribution and excretion of radiotracer amounts of the lanthanons in animals and in man.

The toxicologic information on the distribution and metabolism of radiotracer doses, however, cannot be used with the desired assurance in application to possible health hazards to man. It has been pointed out (15) that conclusions from tracer studies of biologic distribution of radioisotopes cannot always be extrapolated to the dosage ranges of interest to toxicologists and industrial hygienists. For this reason most, if not all, of the large amount of data on distribution and excretion of radioisotopes of the rare earths is of little value in determining fate of the rare earths following their inhalation by man. For this reason only brief reference is given to the metabolism of the radiolanthanons. There is great need for similar information on realistic exposure concentrations of the stable lanthanons.

Essentially, all of the important information on the metabolic properties of the radiolanthanons alone or their chelated complexes is to be found either in Kyker and Anderson (14) or in Hamilton's review (16).

SUGGESTED PROGRAM OF TOXICOLOGIC RESEARCH ON THE LANTHANONS

It is obvious from the above very brief but inclusive literature survey that the needed toxicologic information on stable lanthanons to determine safe practices of handling these substances is nonexistent. Estimates of the hazards from inhalation, chiefly, and also by skin and eye+ should be made. Accordingly, the following research program in inhalation toxicology is suggested as the important initial step.

Priority Substances for Study. On the basis of present and near-future use, the following six elements are given highest priority: Y*, Gd, Eu, Sm, Sc*, Dy.

Present methods of use involve handling the following compound types:

Soluble Forms	Insoluble Forms
Chloride	Fluoride
Bromide	Oxalate
Iodide	Metal
EDTA Chelate	Oxide
	Hydride
	Dioctylphosphate

Levels of Exposure: Irrespective of the number of substances to be studied, a minimum of two exposure levels per substance is required, one, designed to result in a "no effect" response as determined

+ Investigation should be made whether the study of effects of the lanthanons on the eye begun in 1954 by Grant & Kern, Department of Opthalmology, Harvard University, has resulted in the type of information required to determine the hazards to the eye from industrial exposure.

* Not a lanthanon

by the most sensitive and early indicators of metabolic derangement available, the other, a "borderline" response in which mild changes occur in some of the exposed animals. Such information permits an estimate of the degree of safety expected above the "no effect" level.

Suggested Procedure. It is obvious from the number of elements and compounds, the minimum requirement of two test levels and the long-term and costly nature of inhalation studies, that considerable selection and compromise must be made. All elements and their compounds cannot be reasonably tested. Selection might be made on one of the following bases or combinations of them.

A. Chronic - Two-year, Large-Scale Inhalation Exposure

I. All six elements, studied as one insoluble form (oxide)

One soluble form (the chloride or nitrate, whichever is the easier to handle)

At two exposure levels each -

Total number two year studies - 24

II. Element representative toxicologically and otherwise of the six priority elements to be studied in all its used compound types at two levels each.

Total number two year studies - 20

B. Chronic, two-year Small Scale, Dosimetric Method

Studies patterned after AI or II or combination of both.

Procedure B has been suggested by Dr. Harold Hodge as a means of reducing the large costs of test materials. The basis of this procedure is the intensive study of a few animals rather than statistical numbers less extensively studied. Each procedure has advantages and disadvantages in application to the present problem that must be carefully weighed before initiating the work. The choice between them would be determined by the final scope and objectives of the program.

Proposed Research Contractors. It is apparent from the above program outline that any inhalation toxicity study of the lanthanons is of considerable magnitude. Because of its scope and importance, it would seem best to apportion the work among several investigators. Suggested investigators and relative magnitude of effort is given below:

1. Dr. Joseph G. Graca, Assistant Professor Veterinary Physiology and Pharmacology, Iowa State College -
   $100,000 - $150,000* per annum
2. Dr. H. E. Stokinger, Chief, Toxicologic Services - USPHS Occupational Health Field Headquarters, Cincinnati, Ohio.
   $100,000 - $150,000 per annum
3. Dr. Harold C. Hodge, Professor of Pharmacology and Toxicology. University of Rochester School of Medicine - $75,000 per annum.

Both investigators No. 2 and 3 have large and small exposure chambers available for pursuit of the work if program is pursued by procedures AI and AII; if by procedure B, all 3 investigators would probably have to construct special chambers for the purpose; the cost of these chambers would not be large, (below $5,000 each). Additional staff would have to be procured probably by all three investigators and investigator No. 1 will have to provide exposure chambers.

* Note: One pound of certain lanthanon salts may cost from $1,000 to $20,000

H. E. Stokinger, Ph.D.
Chief, Toxicologic Services

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