Fluoride Poisoning:

A Puzzle with Hidden Pieces

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Key industry data regarding harm from chronically inhaled fluoride have been unavailable publicly for decades. Recent unveiling of unpublished reports reveals three examples of data mishandling that disguised the need for more stringent occupational standards for particulate and gaseous fluorides and fluorine. Injury reports from workers handling chemicals show that unjustifiable reductions of injury and disability numbers in the process of publication shifted concern from respiratory to mineralized tissue damage. Selective editing and data omissions allowed bias that fluoride reduces caries without detrimental effects. Finally, industry's failure to publish an important industry-funded laboratory study buried knowledge of low thresholds for fluoride-induced lung disease. Data from that study are presented to clarify the dose- and duration-dependent changes caused by chronic inhalation of calcium fluoride. *Key words*: fluorides; fluorine; chronic inhalation; respiratory injury; occupational standard.

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A history of enigmatic descriptions of fluoride poisoning in the medical literature has allowed it to become one of the most misunderstood, misdiagnosed, and misrepresented health problems in the United States today. Records of acute fluoride poisoning cases compiled between the late 1800s and 1955[1,2] demonstrated that the number of fluoride fatalities was on the rise during that period, probably due to better identification of such cases, improved recording of mortality statistics, and the wider industrial and domestic use of fluoride. Cases in these records predominantly involved suicides or accidental oral overdoses from fluoride mistaken for a food product (i.e., flour, powdered sugar, or milk). Fatalities caused by inhalation or dermal exposure were less frequent and usually linked to industrial accidents in which workers were handling fluorine (F_2) or fluorine compounds that release the fluoride ion, such as cryolite (Na_3AlF_6), uranium hexafluoride (UF_6), hydrogen fluoride (HF), sodium fluoride (NaF), hydrofluoric acid, phosphate rock, and fluorspar (CaF_2). In 1965, fluoride was found to be the cause of about 1% of all the poisoning deaths in the United States.[2] The actual percentage today, however, is unknown, because fluoride, of all the inorganic substances, is among the least likely to be identified by a routine toxicological analysis.[3] When the cause of a fatality is obscure and there is a positive history of exposure to fluoride, fluoride poisoning should be suspected first.

Excessive fluoride exposures have been linked to certain occupations (welding, aluminum work, water treatment, etc.) for decades. The occupational standards for fluorides and fluorine in the United States were originally based on very few laboratory animal studies. A 1909 study by Ronzani,[4] credited as being the original basis for the fluoride standard,[2] found no injuries in rabbits, guinea pigs, and doves exposed to hydrogen fluoride at 2.5 mg /m^3 for 30 days.

In 1943, Largent described the extensive need for fluorine compounds in industrial processes, and used fluorspar consumption as a measure of an industry's potential for occupational hazards.[5] Industry provided ample opportunity for fatal and nonfatal respiratory injury and skin burns from excessive fluoride in the work atmosphere.[1,2,6,7] Largent, however, surmised that industry-related acute fluoride poisoning was "widely known" and warranted "no particular emphasis." Instead, he viewed chronic fluoride poisoning and effects on bone as the bigger concern for industry. Deleterious effects on bone were specific to fluoride, whereas respiratory injuries were not. Any of several coexisting contaminants with established records as respiratory irritants (sulfur dioxide, polycyclic aromatic hydrocarbons, etc.) could be blamed instead of fluoride.[5,8,9]

In 1949, Stokinger[10] found only "minor pulmonary changes" in one of five dogs exposed to 7 mg HF/m^3 for 35 days, and pulmonary hemorrhage and edema in two of five dogs exposed to 3 mg F_2/m^3 for 31 days. While the Ronzani and Stokinger studies exposed animals to gaseous fluorine and hydrogen fluoride, laboratory studies that exposed animals to particulate fluorides were never done.[11] For almost 20 years, Stokinger's data[10] served as the basis for a fluorine threshold limit value of 0.1 ppm.

Not until 1961 did Largent expose five men to hydrogen fluoride in a laboratory setting and establish the fact that gaseous fluoride alone irritated the skin,

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eyes, and nose at concentrations averaging 2.1 to 3.9 mg/m^3 for 50 days.[12] This irritation was reported as slight, temporary, and unaccompanied by symptoms or signs of lower respiratory tract irritation. Largent's 1961 study became the ". . . most relevant in establishing an environmental limit to prevent irritant effects."[13]

The occupational standard for fluorine was relaxed to 1 ppm in 1973 on the basis of findings from two different studies.[14] The most important data came from a 1962 study that found no health problems among 61 workers exposed to a yearly average of 0.3 to 1.4 ppm F_2.[15] A minor basis for upwardly revising the standard came from a 1969 laboratory study of animals that reported evidence of fluorine tolerance.[16] Tolerance in this instance meant rabbits pre-exposed to fluorine (50 ppm for 30 minutes one day per week for four weeks) took longer to die (48 instead of 18 hours) when they were exposed to lethal fluorine concentrations. No mechanism for the tolerance was ever identified, and therefore, this animal study was minimal justification for relaxing the fluorine standard.

With respiratory irritation dismissed as minor, fluoride effects on bone emerged as the focus for occupational standards. This switch was bolstered later by Hodge and Smith's claim in 1977 that greater fluoride exposures were needed to affect the respiratory system than to cause skeletal fluorosis.[17] Thus, threshold limit values (TLVs) in the United States for fluoride dusts and hydrogen fluoride were first set at about 2.5 mg/m^3 in 1948,[18,19] and they were maintained at that level primarily because of the finding that hydrogen fluoride exposures averaging 3.38 mg fluoride/m^3 and above affected bone.[20] The 2.5 mg/m^3 standard was touted as adequate prevention against the hazards of fluoride during the working lifetime.

As this record shows, the occupational standard for fluorides in the United States has not changed to any major extent since the late 1940s,[18] and the standard for fluorine was relaxed over 30 years ago.[14] Only recently have data become available suggesting not only that these standards have provided inadequate protection to workers exposed to fluorine and fluorides, but that for decades industry has possessed the information necessary to identify the standards' inadequacy and to set more protective threshold levels of exposure.

The purpose of this analysis is to present the industry data that should have influenced standard selection years ago. These data establish that gaseous and particulate fluorides are respiratory irritants, that they are deleterious to the respiratory system at exposure levels lower than those affecting bone, and that they alone can cause serious long-term changes that relate to clinical disease. Three examples of industry attempts to keep regulatory focus away from fluoride are presented. All three examples concern the failure to publish important data in the open medical literature. The health effects discussed are all due to inhalation and dermal exposures to various fluorine chemicals. The first and second examples compare published and unpublished injury reports among workers handling chemicals needed for the development of atomic energy. Some of this information was classified as secret for several years, and thus was not available for open review by health professionals. The third example concerns the effects of particulate fluoride on dogs in a laboratory study funded, but never published, by a group of fluoride industries. Data from these three examples fill a critical void in the understanding of fluoride toxicity.

PUZZLE PIECE ONE: GASEOUS FLUORIDES

Comparison of Classified (Unpublished) Industry Data with Published Data

In 1949 a report (hereafter the 1949 Report) was published that described two serious accidents leading to acute fluoride poisonings in the United States.[21] The accidents involved workers handling uranium hexafluoride (UF_6) for the development of atomic energy for military purposes under the Manhattan Project, a highly classified United States military project that would later unveil the first atomic bomb. The report also described studies of chronic exposures to uranium compounds, studies that were distinguished as being more important because they investigated the chronic problems encountered by workers in the laboratories and plants of the Manhattan Project. Due to national security concerns and the highly classified nature of the project, however, no specific data were given about the workers at any laboratory or plant described in the report, even given two years of operational observation. Whereas details in this 1949 Report were intentionally left vague for reasons of national security, the report's conclusions were clear, in that they denied any evidence of chronic fluoride toxicity among workers employed in any phase of the uranium industry (p. 993).

The published 1949 Report described two accidental overexposures to UF_6. As with most accidents, the overexposures were uncertain in regard to the atmospheric concentration and composition at the time of the accident. The first accident involved heat and moisture (steam) along with UF_6, such that it was reasonable to assume that exposure included a mixture of UF_6 and decomposition products of hydrofluoric acid and uranium oxyfluoride. Two workers nearest the explosion died, while three others suffered "serious" injury. Thirteen additional workers were injured slightly but were back to work within 48 hours. Proximity to the explosion determined the seriousness of the injury.

A second accident involving a UF_6 leak resulted in the hospitalization of another worker. Both accidents were categorized as acute, high-concentration exposures of short duration (seconds to minutes) that led to

TABLE 1 Summary of Chemical Hazards from Unpublished[22] and Published[21] Sources

Material	Personnel Exposed	Total Injuries	Disabling Injuries
Uranium hexafluoride (UF_6)[22]	3,050	392	9
Uranium hexafluoride (UF_6)[21]	22	19	19
Fluorine (F_2)[22]	280	58	3
Hydrogen fluoride (HF)[22]	125	21	0
Fluorocarbons[22]	2,220	6	0
Fluorine (phosgene analogs)[22]	50	5	0
Radium[22]	75	0	0
Uranium compounds[22]	3,050	0	0
Uranium 235[22]	650	0	0
Uranium oxide and other uranium compounds[22]	25	0	0
Dry ice; dry ice–trichlor mixture; liquid nitrogen[22]	265	81	0
Chlorine[22]	40	10	0
Trichlorethylene[22]	855	92	1
Carbon tetrachloride[22]	220	22	0
Mercury[22]	650	7	0
Acids[22] (nitric, sulfuric, hydrochloric, chromic, etc.)	485	99	2
Caustic soda and potash[22]	408	17	1
Lime (slaked) [22]	10	2	2
Ammonia[22]	30	5	0

corrosive damage to the skin, eyes, and respiratory mucosa due to the fluoride ion and temporary kidney changes due to uranium. Whether the outcome was fatal or nonfatal, fluoride affected the lungs, causing a range of changes from edema to transient symptoms of respiratory distress such as coughing spells, shortness of breath, and chest rales. Such changes emerged frequently in the pathology findings and/or physical examinations administered by clinicians.

The published 1949 Report cast a very different light on chronic exposures to uranium compounds seen at plants and laboratories under the Manhattan Project operation. For purposes of security, only vague details were given about the atmospheric work environment and the number of workers exposed. Enforcement of a "full-time safety program," precautionary handling procedures, and monitoring schedules for uranium and radiation at each facility gave the impression of control over exposures to hazardous material. Such controls appeared effective because no toxic changes of any kind were reported for workers handling uranium compounds for several months.

To rule out the possibility that the methods for detection were too insensitive to reveal an effect, the workers were subjected to a battery of examinations. These examinations were to provide the most sensitive index of injury to humans, test for all physical effects linked to uranium compounds, fit simply into routine clinical analyses, and apply to all types of individuals without alerting them to a problem. In reality, the testing was a serial examination of blood and urine samples at specific intervals, tests that would detect changes specific to uranium but not to fluoride. A fluoride effect on the respiratory system, an effect prominently linked to acute high-concentration exposures, was in no way associated with the exposures of workers handling uranium compounds on a daily basis.

In 1997, the Department of Energy declassified an unpublished 1946 industrial injury report (hereafter the 1946 Report) concerning workers handling UF_6 at one of the plants involved in the Manhattan Project.[22] This 1946 report was provided to the District Engineer of the Manhattan Project operation in Oak Ridge, Tennessee, by a Manhattan Project plant superintendent in response to a request for information regarding special occupational hazards and response methods. The report summarized injuries and lost work time caused by exposure to each type of chemical material used in the plant for the period of October 1944 to October 1946.

Data from the unpublished 1946 Report fill gaps left by the published 1949 Report regarding the hazards of the uranium industry and its relationship to fluoride poisoning.

Exposures and Related Health Effects According to the 1946 and 1949 Reports

The 1946 Report from the medical department of one Manhattan Project plant demonstrated that the 1949 published Report was misleading about the hazards of the uranium industry and its relationship to fluoride poisoning. It also proves that the subsequent report was misleading in regard to the hazards of handling uranium compounds. Data from the 1946 report are shown in Table 1, where the number of personnel exposed, total injuries, and disabling injuries are listed for each chemical or chemical category. The data show that total injuries combined for fluorine and related compounds (F_2, UF_6, HF, fluorine phosgene analogs, and fluorocarbons) were greater than those for all other chemicals combined. Likewise, disabling injuries occurred more frequently among personnel exposed

TABLE 2 Disabling Injuries from Uranium Hexafluoride and Fluorine

Material	Type/Degree of Disability	Cause of Injury	Days off Work
Uranium hexafluoride (UF_6) (Unpublished[22]) Total = 9 cases	Respiratory irritation Temporary/total (6 cases)	Misoperation	1 (3 cases)
		Faulty equipment	2
		Unsafe procedure	39
	Combined with infection	Failure to wear mask	52
	Respiratory damage Permanent/partial (1 case)	Failure to wear mask	293
	Dermatitis on face Temporary/total (1 case)	Wore contaminated mask	9
	Burn on hand Temporary/total (1 case)	Failure to wear gloves	3
Fluorine (F_2) (Unpublished[22]) Total = 3 cases	Respiratory irritation Temporary/total (2 cases)	Leak, unknown origin	2
	Complicated by infection	Failure to wear mask	2
	Eyes and throat Inflamed Temporary/total (1 case)	Unsafe procedure Unsafe equipment	1
Uranium hexafluoride (UF_6) (Published[21]) Total = 19 cases	Death (2 cases)	Rupture of storage tank/ steam line Cylinder leak	Lifetime (2 cases)
	Respiratory irritation		2 (13 cases)
	Burns (eyes and skin)		14 (?) (3 cases)
	Gastrointestinal/nervous/ urinary changes Temporary (17 cases)		30 (?) (1 case)

to F_2 and UF_6 than among those exposed to all other chemicals combined. While the 1949 Report focused on the hazards of handling radioactive material, the 1946 Report listed zero injuries for personnel handling radium, uranium compounds, uranium 235, uranium oxide, and other uranium compounds. The 1946 Report also explained each disabling injury from F_2 and UF_6 according to its type, degree, cause, and days off work, as shown in Table 2 for F_2 and UF_6. All but two of these disabling injuries (a burn and dermatitis) involved respiratory tract irritation, inflammation, or infection. The disabling injuries caused by other chemicals (not shown in Table 2) were conjunctivitis (from trichloroethylene or slaked lime), burns (from caustic soda or chromic acid), and dermatitis (from chromic acid). The disabling injuries caused by all chemicals were labeled as "temporary total," except for one "permanent partial" injury from UF_6 that prevented an employee from working for over nine months due to respiratory damage. Failure to wear a mask was given as the cause of most disabling respiratory injuries.

Relevance to Occupational Safety Standards of the 1946 and 1949 Reports

The 1946 and 1949 Reports provide information about human exposures to fluorine and fluorine compounds that is applicable to current safety standards set for UF_6, F_2, and HF. Such human exposure data are rare, and despite their limitations, these reports give a perspective on industrial fluoride exposure unattainable from laboratory studies of animals. The 1946 and 1949 Reports do not define exposure concentrations or durations with any precision, nor do they reveal whether or not the injuries were suffered repeatedly by certain individuals or by various individuals. A longitudinal study design, the most reliable method for study of risks,[8] was not possible given the rapid turnover of employees in wartime conditions, and the periods of observation of the personnel were no more than about two years according to both the 1946 and 1949 Reports, hardly the working lifetime that current standards must address. Despite the limitations of these data, however, the data were recognized as significant. The 1946 Report recommended that there be an exchange of medical information between the various units of the Manhattan Project. Such an exchange does not appear to have occurred, nor was the information ever transferred to the entire medical community.

Uranium hexafluoride. The 1949 Report concluded that the standard of 150 μg uranium dust/m^3 of factory air was sufficient to protect the UF_6 worker in the uranium industry (p. 1016). In particular, the standard protected workers from the kidney and radiation

damage peculiar to uranium. In contrast, the 1946 Report revealed that that standard was in use at the plant when 392 injuries occurred among 3,050 workers exposed (about 13%). Nine of the injuries were "disabling" and due most often to respiratory problems, a recognized fluoride effect at the time. The 1949 Report referred only to injuries caused by sudden explosions and leaks, with no indication of any day-to-day problem in the work environment. The 1946 Report revealed that routine failure to wear a mask, rather than rare explosions, had caused most injuries. Moreover, the injuries, or in some cases just exposures, brought numerous workers to the dispensary, and disabling injuries were occurring almost monthly. Because many of these injuries were due to fluoride exposure, a standard for the uranium industry must focus on fluoride as much as on uranium if it is to protect the worker.

Fluorine. The 1949 Report did not mention injuries to employees exposed solely to F_2. According to the 1946 Report, however, F_2 was expected to irritate the respiratory tract and cause severe external burns, necessitating enforcement at the plant of a maximum allowable concentration of 3 ppm for prolonged exposures. The odor of F_2 was detected at 0.1 ppm. Despite the precautions, almost 21% of the workers handling F_2 (58 out of 280 exposed) were listed as injured, of whom three were disabled and temporarily incapable of performing their duties.

As previously mentioned, the occupational standard for fluorine was relaxed from 0.1 to 1 ppm in 1973[14] based primarily on data from the 1962 study of 61 workers exposed to a yearly average of 0.3 to 1.4 ppm F_2.[15] No increase in the incidence of respiratory complaints was found among the 61 exposed workers, compared with 2,000–3,000 unexposed plant employees. This 1962 study concluded with the statement: "[n] o impairment to health of people working in fluorine concentrations probably considerably in excess of 0.1 ppm has been demonstrable from their medical records at this installation." This particular 1962 study, however, came from the same industry that produced the 1946 Report, but it covered data from 1952 to 1959 and ignored the data from six to eight years earlier. The respiratory injuries of the 58 F_2 workers mentioned in the 1946 Report were swept under the table, clearing the way for data more supportive of a relaxed occupational standard.

Hydrogen fluoride. The 1949 Report did not reveal any information regarding the 125 individuals who had been exposed to HF when the maximum allowable concentration enforced in the plant was 3 ppm (about 2.5 mg/m^3). The 1946 Report listed 21 injuries among the 125 workers exposed. The 21 injuries meant 21 trips to the dispensary if for nothing else than to report an exposure. These data also indicate that Largent's 1961 study of five human volunteers exposed to hydrogen fluoride[12] was neither the first nor the largest data set available for assessing the risks to humans of repetitive exposure to low levels of HF. The exposure period examined by Largent was 50 days, whereas the 1946 Report covered two years. Occupational standards are supposed to protect individuals for a working lifetime. The injured workers in the 1946 Report would present a clearer picture of what to expect from a working lifetime of repetitive, mild respiratory irritations relative to clinical disease.

PUZZLE PIECE TWO: HYDROFLUORIC ACID

Published and Unpublished Versions of Data

Dental conditions of men continuously exposed to hydrofluoric acid were examined under the Manhattan Project and published in the *Journal of the American Dental Association* ("JADA") in 1948.[23] The subjects were employees at a chemical company where the atmosphere was so contaminated it could etch windows and eyeglass lenses, dehydrate animate surfaces, kill microorganisms, disintegrate leather shoes, and repel animals from the vicinity. Despite this bleak working environment, the workers were described in the following manner: "On the whole, employees working with the hydrofluoric acid appeared to be unusually healthy men, physically sound and comparatively immune to colds, infections and other common illnesses."

The published JADA article consisted of excerpts from a series of unpublished classified reports that started in 1943.[24–28] The reports described the workers' dentition, urinary fluoride levels, and bone changes detected by roentgenography. No quantitative determinations of contaminant levels were ever revealed. It was concluded that hydrofluoric acid exposure lowered the incidence of caries, increased urinary fluoride, and altered the trabecular bone pattern in the jaws of workers without causing sclerosis or general bone disease.

Differences between Published and Unpublished Reports

The unpublished reports[24–28] gave a more balanced view of the findings than did the published JADA article.[23] For example, the JADA article emphasized that the workers had fewer filled and carious teeth, but the unpublished reports added the qualifier that fewer carious teeth might be due to having fewer teeth overall. Exposed workers tended to be edentulous, or nearly so, and the unpublished reports admitted that acid exposure, along with age, might have contributed to this unusual attrition as it etched and polished some of the teeth. Deterioration of teeth, from "highly polished and glasslike" to "dull with a peculiar brownish deposit which seemed to cover the enamel of the anterior teeth in especially large quantity," was a process that should have been investigated as an occupational hazard. Instead, the JADA article[23] falsely linked the highly pol-

ished glass appearance of teeth to a "clean mouth" and the dull, brown deposits on teeth to a "neglected mouth." This distinction based on oral hygiene was not in the unpublished reports. On the contrary, the unpublished reports indicated that most men in the group examined practiced poor oral hygiene and chewed tobacco, and that periodontoclasia was common in both exposed and control groups. Thus, there was no scientific basis for the JADA article to shift the blame for the brown deposits on teeth from the hydrofluoric acid exposure to the workers' poor oral hygiene practices.

Another example of misrepresentation by the JADA article concerned the bone changes in the jaws of the workers. One unpublished report[26] clarified that the trabecular changes observed in the mandibular and maxillary bones of the workers produced an apparent increase in the bone density (sclerosis) of the jaw. The "no sclerosis" claim by the JADA article should have been restricted to areas of the body other than the jaw. More appropriately, however, the "no sclerosis" claim should have been omitted from the JADA article altogether, because examination of one of the exposed workers four years later demonstrated that practically all the bones of his skeleton were sclerotic.[23]

Evidence of a more serious problem with the Manhattan Project dental study can be found in both the published and the unpublished versions of the results. The problem concerns the number of subjects and their classification as being "exposed" or "control." The JADA article[23] indicated that 51 men were examined: 35 were exposed; 11 were controls; and five were excluded. The label of "exposed" or "control" was assigned haphazardly and did not fit the data presented in Tables 1 and 2. For example, case 20 was listed as "unexposed" in Table 2 (and the Table 2 legend) and had a urinary fluoride level in the control range (< 1 mg F/L urine), but was included in the "exposed" data in Table 1.[23,24] Case 46 was a "control" even though he was occasionally exposed to hydrofluoric acid while working in a nearby warehouse and had a urinary fluoride level in the range associated with the "exposed" group (1.70–49.3 mg F/L urine). Cases 36 to 40 were excluded because they had had dental defects prior to exposure and had been employed for only one to three years.[23] However, the time span of employment was actually two to six years, bringing into question the timing of the dental defects with respect to the onset of exposure. The urinary fluoride levels of all excluded cases were in the "exposed" range. In addition to the five cases that were specifically mentioned as being excluded, other cases may have been excluded without proper justification. The legend of Table 2 in one unpublished report gave case numbers up to 57,[24] but no reason was given for omission of cases beyond the original five exclusions. Thus, the methods for subject classification were not of a caliber to warrant confidence in the conclusions or dismiss tooth deterioration and loss as a consequence of something other than occupational hydrofluoric acid exposure.

Early Data Distortion Leads to Current Bias

Workers at a chemical plant with a heavily contaminated atmosphere were not the logical choice for controls in a dental study, regardless of the job description. Without data confirming contaminant levels in the breathing spaces of individual employees, classifying subjects as exposed or control was guesswork. This serious flaw was recognized years ago. In a 1944 memorandum sent to the U.S. Engineer Office of the Manhattan Project,[29] it was acknowledged that there was a need for suitable controls to complete the study of dental problems among workers at the chemical plant. In the memorandum it was stated: "This suggestion may have merit but will be rather difficult to carry out unobtrusively because no suitable controls are available in plants working on District projects." The proposed work was thought to have "considerable academic interest" but no ". . . immediate, practical importance," so it was given a low priority. To date, this dental study lacks proper controls, hides evidence of tooth destruction and loss, and stays in the literature as invalid proof of caries reduction by fluoride. Animal studies in 1934, prior to the Manhattan Project dental study, demonstrated that ingested fluoride caused teeth to break or loosen in their sockets.[30] Moreover, recent clinical studies of humans have linked fluoride with tissue necrosis and permanent loss of periodontal alveolar bone.[31] In spite of this evidence, the severe dental problems of fluoride workers are conveniently attributed to tobacco use or poor oral hygiene, and the claims for compensation to correct the problems are unjustifiably denied.[32] There are many studies in the medical literature that link dental problems with tobacco use and poor oral hygiene, but studies that link dental problems with fluoride in the workplace have yet to get past "low priority."

PUZZLE PIECE THREE: PARTICULATE FLUORIDE

Unpublished Research Funded by Industry

A litigation research group formed by various industries sponsored studies of the health effects of occupational exposure to particulate fluorides in the early 1960s.[33,34] The importance of these studies to industry was explained by a scientist overseeing the work[34]: "Despite the fact that the further litigation which was anticipated with apprehension some years ago has failed to appear, the industries involved are vulnerable in the field of occupational disease hazard and in the field of community health relating to air pollution.

TABLE 3 Design Features of the Inhalation Study of Davis et al.[35]

Exposure	Reagent grade CaF_2 Inhalation chamber (minimal ingestion) Intermittent (6 hrs/day; 5 days/week) Concentrations (0.56 μm particle size): ≤ 0.97 (control), 3.5 (low dose) or 35.5 mg F/m^3 (high dose) One year duration
Animals	Female beagle dogs (12.5–16.5 months old)
Tests	Scheduled at 2, 4, 6, 8, 10, 12 months and 6 months post exposure
1. Physical examination	Daily checks of nutritional status, reflexes, behavior and appearance
2. Body weight and food consumption	Checked weekly
3. Respiratory rate	During exposures
3. Gross and microscopic pathology	All tissues, including lungs, brain, spinal cord, pituitary, parathyroid, thyroid, adrenals, heart, kidney, liver, and ovaries
3. Fluoride levels	Tissues, blood, urine, feces, nails, and spinal fluid
4. Blood measures	Before, during, and after exposure—leukocyte and erythrocyte counts, hemoglobin, hematocrit, pyrophosphatase, glucose, total protein, urea nitrogen, inorganic phosphate, calcium
5. Urine measures	Protein, ketone, bilirubin, sugar, albumin, blood *p*H, specific gravity
6. X-rays	Entire skeleton, lungs, trachea

This vulnerability will continue to exist until there is a further elucidation of the human manifestations of fluorosis. The means of investigating this matter, as we have pointed out previously, is in industry."

Industry indeed funded a critical laboratory study in 1962 by Davis et al.[35] that investigated the physiologic effects of chronic inhalation of a fluoride dust, calcium fluoride (CaF_2). The design features and results of this study are shown in Tables 3 and 4, respectively. Although the effects of fluoride ingestion were also examined in a parallel study, Tables 3 and 4 focus on the consequences of inhaling fluoride, the route of exposure most relevant to the occupational setting. Overall, the study had a comprehensive design approach that few laboratories were equipped to handle. In specially designed inhalation chambers, dogs inhaled CaF_2 dust with particles small enough to distribute into the pulmonary air sacs and alveoli, where it was being absorbed at an appreciable rate. The extent of this lung absorption was reflected by fluoride levels in the urine and other tissues, levels that increased proportionately to the dose and duration of exposure. Six months after cessation of exposure, absorption, redistribution and excretion of fluoride continued because of storage in the lymph nodes. Since the lymph nodes acted as a fluoride reservoir that slowed absorption and delayed recovery, the balance of fluoride input and output was more difficult to achieve when exposure was by inhalation than by ingestion. By six months after exposure, fluoride levels in the lungs had decreased while levels in the skeleton still increased.

As shown in Table 4, the deleterious consequences of inhaled fluoride were found in the study to be limited to the lungs and lymph nodes and detectable only by post-mortem gross and microscopic examination. The disproportional increase in lung weight (relative to body weight gain) in the exposed dogs was due to thickened alveolar walls, fibrosis, and alveolar exudation. Both the low and high fluoride doses caused peribronchitis with infiltration by lymphocytes and macrophages. With time, the cellular infiltrates were gradually replaced by fibrous tissue. In addition, the bronchial epithelium was hyperplastic, whereas the musculature of the bronchioli was hypertrophic and progressively fibrotic. Lymphatic tissues enlarged, then diminished over time, becoming increasingly firm, and were eventually replaced by foreign material. The high dose produced essentially the same changes but to a greater extent and in a shorter time. Two pathologic changes, granulomatous lesions and pleural fibrosis, were seen only in the high dose animals. Just two months of exposure to the high dose produced marginal pulmonary emphysema.

Importance of the Unpublished Industry Research on Chronic Fluoride Inhalation

This unique dog study by Davis et al.[35] expands the understanding of chronic fluoride poisoning by inhalation. It spotlighted the lungs as an important site for fluoride absorption by demonstrating that equal urinary fluoride levels could be achieved when 35.5 mg F/m^3 were inhaled and when 167 mg CaF_2 were ingested on a daily basis. It pointed to the lungs and regional lymph nodes as the sole targets for destruction when fluoride was inhaled but not ingested. Several years later, other

TABLE 4 Summary of Inhalation Exposure Results Found by Davis et al.[35]

Physical examination	Normal
Respiratory rate	Normal
Body weight gain and food consumption	Normal
Urine measures	Normal
Blood measures	Normal
Fluoride levels	Dose/time-related increases in urine, feces, and body burden; blood was an erratic indicator; tissue levels: skeleton > kidneys > liver, bile, salivary glands, mesenteric lymph nodes, spinal fluid > blood
X-rays	Normal skeleton and teeth
Gross and microscopic pathology	Normal viscera except for lungs and regional lymph nodes; lung weight gain > body weight gain
	Controls: pneumonitis by 6 months; mononuclear cell infiltration; chronic inflammation in tracheal lymph nodes
	Low dose: Peribronchitis at 2 months; lung consistency change, subpleural nodulation, monocytic aggregation with time; at 6 months, altered bronchial epithelium and musculature; at 8 months, fibrosis, enlarged lymph nodes; at 12 months, increased lung weight, granular intra-alveolar transudate, lymph nodes hyperplastic and gathering foreign material
	High dose: Peribronchitis as with low dose but more severe and appearing sooner; at 2 months, trachea lymph nodes enlarged, granulomatous lesions; at 6 months, increased lung weight, fibrosis, foreign material in lymph nodes; at 10 months, lung tissue consolidation, pleural fibrosis, fibroblasts appeared; at 12 months, lungs fleshy, dull red, granular pleural surfaces

animal studies found the lungs to be at risk for emphysema even when the primary route of exposure was ingestion.[36] The disproportional increase in lung weight observed in the dog study[35] was similar to that found recently in other animal studies of the respiratory effects of fluoride.[37] The Davis et al. dog study documented that inhaling fluoride caused pulmonary cellular alterations, which recent studies have linked to a diminished ability to cope with infectious bacteria.[38] Finally, the Davis et al. study followed the year-long progression of fluoride-induced inflammation in the lungs, a process observed in current studies as starting in humans when they inhale fluoride for as little as one hour.[39,40] In general, past and present studies converge as to the type of respiratory damage caused by fluoride, inflammation and emphysema, and the current research serves as a confirmation of the work that was performed decades earlier but never published.

The 12-month exposure and the six-month recovery period distinguish the Davis et al. study from all other animal studies of chronic fluoride inhalation. Exposures in other studies typically lasted 14 to 35 days, the dose range was 0 to 13.3 mg F/m^3, and significant respiratory effects started at 5 to 7 mg/m^3.[4,10,37,38] The dose range of the Davis et al. study was ≤ 0.97 (control) to 35.5 mg F/m^3, and significant pulmonary abnormalities were detected at ≥ 3.5 mg F/m^3. However, two observations made by Davis and his colleagues undermined confidence in designating doses lower than 3.5 mg F/m^3 as the "no effect" level. First, the similar pathologic changes observed at the low (3.5 mg/m^3) and high doses were dose- and duration-dependent. The fact that granulomatous lesions and pleural fibrosis were seen only at the high dose was likely due to the "brevity of experiment," such that they might also have developed at lower doses had the exposure duration been extended beyond 12 months, as is encountered in actual occupational exposures. The second observation countering a 3.5 mg F/m^3 threshold for effects was the fact that Davis et al. found the lungs of controls to be abnormal. The controls were exposed to ≤ 0.97 mg F/m^3, but after six months of exposure, their lungs showed pneumonitis, mononuclear cell infiltration, and tracheal lymph node inflammation. In addition, fluoride excretion (in urine and feces) increased in the control animals as exposure was continued, and low levels of fluoride were found in their lungs at necropsy. Therefore, some air-borne fluoride contamination reached the control animals despite precautions to prevent cross contamination, and the "control group" then was not a true control but a "baseline" for the other exposure groups. Thus, to have confidence in a no-effect level, exposures at or less than 0.97 mg F/m^3 for durations longer than 12 months must be examined.

One more, and perhaps the most important, feature of the Davis et al. study concerned the type of fluoride to which the dogs were exposed, reagent-grade CaF_2. Use of reagent-grade CaF_2 avoided confusion as to the chemical species causing harm and the consistency of the exposure across treatment groups. Naturally occurring fluorides such as rock phosphates or cryolites (as well as fluoride chemicals derived from them, such as hydrofluosilicic acid) vary considerably in composition, including contaminants (e.g., lead and arsenic). For years, studies of the respiratory problems of aluminum workers and welders were unable to distinguish the fluoride effect from that of sulfur dioxide[8,9,41–44] or hexavalent chromium and isocyanates,[45] respectively. Moreover, as the Davis et al. study was a controlled laboratory investigation of dogs, variables such as smoking, prior disease, and prior occupational exposures were not factors complicating the cause-and-effect picture. Of all the fluorine compounds, CaF_2 is considered to be among the least toxic.[46] Therefore, it is understandable why Davis and his colleagues were surprised to find that CaF_2 caused an active pathologic response instead of a simple reaction to the introduction of a foreign body. Because CaF_2 caused granulomata in an unusual number and location, the fact was established that it was not an inert dust but rather a noxious stimulus similar to compounds with higher toxicity ratings (e.g., hydrogen fluoride and sodium fluoride).

The study by Davis et al. would have made an important contribution to the standard-setting process had it been made available to the medical community earlier. It expands understanding of fluoride's threshold effects well beyond that established originally by Ronzani[4] and Stokinger.[10] In fact, the Davis et al. study provides crucial evidence that unquestionably links respiratory damage to fluoride alone and supports an occupational standard similar to the more stringent levels established abroad.[41,43]

CONCLUSION

Review of unpublished information regarding the effects of chronic inhalation of fluoride and fluorine reveals that current occupational standards provide inadequate protection. Medical information needed to minimize the risks of fluoride poisoning in an occupational setting was kept from the entire medical community. The manipulation and omission of important data set the course for gross underestimation of the number of cases of fluoride poisoning in the United States. Regulatory change is needed immediately to correct past distortions and restore confidence that harmful inhalation exposures to fluoride and fluorine are prevented. The information presented here supports the following changes:

1. *The occupational standard for fluorides should be reduced from 2.5 mg/m^3 to 1.0 mg/m^3 to fit the published and unpublished data regarding respiratory effects.* The evidence presented here confirms that adverse respiratory effects are a product of high-dose accidents and day-to-day industrial exposures despite a 2.5 mg/m^3 fluoride standard. The evidence further shows that fluoride alone can cause respiratory problems separate from sulfur dioxide, uranium, or any other coexisting substance, and a standard protective of workers in the uranium industry must keep focus on the fluoride as much as on the uranium. Industry reports of respiratory injuries among Manhattan Project workers demonstrated that respiratory injuries, some disabling, were occurring at a frequency greater than reported publicly. The respiratory effects were determined by chest x-rays and general physical examinations during a two-year period but not examined years later to discover long-term consequences from on-the-job injury. Such long-term follow-up might have predicted the persistent respiratory problems seen today due to short-term fluoride exposures to household products.[47,48] The laboratory study by Davis et al. clearly linked chronic low-dose fluoride exposure with clinically relevant lung damage that progressed insidiously without disturbing lung function or overall well-being. The animal study further demonstrated lung and lymph node abnormalities at fluoride exposure levels lower than reported elsewhere in the published literature. Given that humans are considered more sensitive to fluorine compounds than experimental animals,[1] the fluoride concentration levels Davis et al. found harmful to animals would not overestimate potential risks for humans. Furthermore, overestimation of risk was not likely, because exposures consisted of fluoride alone and not combinations of contaminants that can interact synergistically, as encountered in the workplace. The chemical mix is an important consideration, in that fluoride can enhance the responses to coexisting chemicals, such as the response to beryllium.[49,50]

2. *The current threshold limit value for fluorine (1 ppm or 1.6 mg/m^3) should be lowered back to the pre-1973 level (0.1 ppm) to fit the published and unpublished data.* As discussed in this paper, the primary data given to support the upward revision of the fluorine standard were seriously flawed by omission of industry records of respiratory injury and disability among Manhattan Project workers. No new laboratory studies of animals have replaced the earlier findings of Stokinger that supported the original 0.1 ppm threshold limit value for fluorine.

3. *Respiratory disorders (e.g., potroom asthma and emphysema) and dental problems (e.g., enamel erosion, periodontal disease, and tooth loss) should be recognized as occupational risks of fluoride exposure and worthy of compensation.* The 2.5 mg/m^3 fluoride standard may have made crippling skeletal fluorosis a rarity in the United States,[2] but respiratory and dental damages have been allowed to slip by unchecked. The buried information revealed here shows that overexposure to fluoride can create prob-

lems for the lungs, lymph nodes, and teeth as much as it does for bone. Fluoride-induced dental problems among workers were effectively hidden behind claims of caries reduction. This deception was achieved by selection of control and exposed subjects from the same heavily contaminated work environment, by misclassification of subjects among control and exposed groups, and by selectively editing reports to deflect blame from fluoride to tobacco and poor oral hygiene. By not making available certain information, the path was cleared for expansion of industrial uses of fluoride at the expense of our ability to prevent, diagnose, and treat fluoride poisoning.

References

1. Roholm K. Fluorine Intoxication. A Clinical–Hygienic Study. London, England: H. K. Lewis and Company, 1937.
2. Hodge HC, Smith FA. In: Simons JH (ed). Fluorine Chemistry. New York: Academic Press, 1965.
3. Moritz AR, Morris RC, Hirsch CS. Handbook of Legal Medicine. St. Louis, MO: C. V. Mosby, 1975.
4. Ronzani E. [Experimental studies of the effect of inhaling irritant industrial gases upon the organism's defense mechanisms against infectious diseases. (partial)] Arch Hyg. 1909; 70: 217-69. [In German]
5. Largent EJ. Fluorides as an industrial health problem. Proceedings of Eighth Annual Meeting of Industrial Hygiene Foundation of America, Pittsburgh, PA, 1943 (Nov).
6. Gelman I. Poisoning by beryllium oxyfluoride. J Ind Hyg Toxicol. 1936;18:371-9.
7. Carlson AJ. Treatment of Hydrofluoric Acid Casualties. Universal Oil Products Company, Chicago, IL, 1943.
8. Kongerud J, Boe J, Soyseth V, Naalsund A, Magnus P. Aluminium potroom asthma: the Norwegian experience. Eur Respir J. 1994;7:165-72.
9. Fritschi L, Sim MR, Forbes A, et al. Respiratory symptoms and lung-function changes with exposure to five substances in aluminium smelters. Int Arch Occup Environ Health. 2003; 76: 103-10.
10. Stokinger HE. Toxicity following inhalation of fluorine and hydrogen fluoride. In: Voegtlin C, Hodge HC (eds). Pharmacology and Toxicology of Uranium Compounds. New York: McGraw Hill, 1949:1021-57.
11. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Fluorides, Hydrogen Fluoride, and Fluorine. U. S. Department of Health and Human Services, Public Health Service, ATSDR, 2003.
12. Largent EJ. Fluorosis: The Health Aspects of Fluorine Compounds. Columbus, OH: Ohio State University Press, 1961.
13. NIOSH. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard . . . Occupational Exposure to Hydrogen Fluoride. DHEW (NIOSH) Pub. No. 76-143; 1976.
14. American Conference of Governmental Industrial Hygienists: Fluorine. Cincinnati, OH: ACGIH, 1992.
15. Lyon JS. Observations on personnel working with fluorine in a gaseous diffusion plant. J Occup Med. 1962;4:199-200.
16. Klepinger ML. Effects from repeated short-term inhalation of fluorine. Toxicol Appl Pharmacol. 1969;14:192-200.
17. Hodge HC, Smith FA. Occupational fluoride exposure. J Occup Med. 1977;19:12-39.
18. American Conference of Governmental Industrial Hygienists: Hydrogen Fluoride. Cincinnati, OH: ACGIH, 2001.
19. U.S. Department of Labor, Occupational Safety and Health Administration, Regulations (Standards-29 CFR), 2002.
20. Derryberry OM, Bartholomew MD, Fleming RBL. Fluoride exposure and worker health. The health status of workers in a fertilizer manufacturing plant in relation to fluoride exposure. Arch Environ Health. 1963; 6: 503-14.
21. Howland JW. Studies on human exposures to uranium compounds. In: Voegtlin, C, Hodge HC (eds). Pharmacology and Toxicology of Uranium Compounds. New York, McGraw Hill, 1949: 993-1017.
22. Center CE (Carbide and Carbon Chemicals Corporation). Letter addressed to the District Engineer, Manhattan Project, Oak Ridge, Tennessee, Attention: Col. Wm. D. Fleming, October 28, 1946.
23. Dale PP, McCauley HB. Dental conditions in workers chronically exposed to dilute and anhydrous hydrofluoric acid. J Am Dent Assoc 1948; 37: 131-40,
24. Dale PP, McCauley HB. Oral conditions in workers chronically exposed to dilute and anhydrous hydrofluoric acid. United States Atomic Energy Commission, University of Rochester, Nov 1944;MDDC-995: 1-8.
25. Dale PP and McCauley HB. A study of dental conditions in workers exposed to dilute and anhydrous hydrofluoric acid in production. Preliminary Report of Oral Examination of Forty-Seven Workers at the Cleveland Plant of the Harshaw Chemical Company. Cleveland, OH, October 13–15, 1943.
26. Dale PP, McCauley HB. A study of dental conditions in workers exposed to dilute and anhydrous hydrofluoric acid in production. Radiographic Findings in Forty-Seven Workers at the Cleveland Plant of the Harshaw Chemical Company. December 31, 1943.
27. Dale PP, McCauley HB. "C" Study. A study of dental conditions in workers exposed to dilute and anhydrous hydrofluoric acid in production. University of Rochester, January 6, 1944.
28. Dale PP, McCauley HB. "C" Study. A study of dental conditions in workers exposed to dilute and anhydrous hydrofluoric acid in production. Statistical Report. University of Rochester, April 1, 1944.
29. Ferry JL (Captain, Medical Corps). Memorandum to Col. Stafford L Warren, U. S. Engineer Office, Oak Ridge, TN. Subject: Proposed Dental Research. May 4, 1944. (Atlanta NARA).
30. DeEds F, Thomas JO. Comparative chronic toxicities of fluorine compounds. Proc Soc Exp Biol Med. 1934; 31:824-5.
31. Sjostrom S, Kalfas S. Tissue necrosis after subgingival irrigation with fluoride solution. J Clin Periodontol. 1999; 26: 257-60.
32. Limeback H, Mullenix P. Occupational risks for dental problems in workers exposed to fluoride. A report of two cases. In preparation.
33. MacMillan JM. (Reynolds Metals Company) Letter to Robert A Kehoe, Kettering Laboratory, University of Cincinnati, Cincinnati, OH, Aug 29, 1961.
34. Kehoe RA. Letter to MacMillan JM, Sept 20, 1961.
35. Davis RK, Stemmer KL, Jolley WP, Larson, EE. The effects of the subjection of dogs to the inhalation and ingestion of calcium fluoride. Unpublished work from the Kettering Laboratory in the Department of Preventive Medicine and Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, OH, 1962. (Kettering Laboratory Library.)
36. Aydin G, Cicek E, Akdogan M, Gokalp O. Histopathological and biochemical changes in lung tissues of rats following administration of fluoride over several generations. J Appl Toxicol 2003; 23:437-46.
37. Chen X-Q, Machida K, Ando M. Effects of fluoride aerosol inhalation on mice. Fluoride. 1999; 2:153-61.
38. Yamamoto S, Katagiri K, Ando M, Chen X-Q. Suppression of pulmonary antibacterial defenses mechanisms and lung damage in mice exposed to fluoride aerosol. J Toxicol Environ Health. 2001;62:485-94.
39. Lund K, Refsnes M, Sandstrom T, et al. Increased CD3 positive cells in bronchoalveolar lavage fluid after hydrogen fluoride inhalation. Scand J Work Environ Health. 1999;25:326-34.
40. Lund K, Refsnes M, Ramis I, et al. Human exposure to hydrogen fluoride induces acute neutrophilic, eicosanoid, and antioxidant changes in nasal lavage fluid. Inhalation Toxicol. 2002;14:119-32.
41. Kongerud J, Samuelsen SO. A longitudinal study of respiratory symptoms in aluminum potroom workers. Am Rev Respir Dis. 1991;144:10-6.
42. Soyseth V, Kongerud J. Prevalence of respiratory disorders among aluminium potroom workers in relation to exposure to fluoride. Br J Ind Med. 1992;49:125-30.

43. Lund K, Ekstrand J, Boe J, Sostrand P, Kongerud J. Exposure to hydrogen fluoride: an experimental study in humans of concentrations of fluoride in plasma, symptoms, and lung function. Occup Environ Med. 1997;54:32-7.
44. Romundstad P, Andersen A, Haldorsen T. Nonmalignant mortality among workers in six Norwegian aluminum plants. Scand J Work Environ Health. 2000;26:470-5.
45. Sjogren B. Fluoride exposure and respiratory symptoms in welders. Int J Occup Environ Health. 2004;10:310-2.
46. Gosselin RE, Hodge HC, Smith RP, Gleason MN. Clinical Toxicology of Commercial Products. Acute Poisoning. 4th ed. Baltimore, MD: Williams and Wilkins, 1976: 78.
47. Bennion J, Franzblau A. Chemical pneumonitis following household exposure to hydrofluoric acid. Am J Ind Med. 1997; 31:474-8.
48. Franzblau A, Sahakian N. Asthma following household exposure to hydrofluoric acid. Am J Ind Med. 2003;44:321-4.
49. Stokinger HE, Ashenburg NJ, DeVoldre J, Scott JK, Smith FA. The enhancing effect of the inhalation of hydrogen fluoride vapor on beryllium sulfate poisoning in animals. University of Rochester Atomic Energy Project, Contract W-7401-eng-49, April 4, 1949.
50. Eisenbud M (Brush Beryllium Company-Luckey Experience). Memorandum to W. B. Harris regarding acute beryllium toxicity. February 27, 1961. (Germantown DOE History Archive.)

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