*Manie P. Currin and Associates*

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BOARD OF SCIENTIFIC COUNSELORS

NATIONAL TOXICOLOGY PROGRAM

# PEER REVIEW OF DRAFT TECHNICAL REPORT OF LONG-TERM TOXICOLOGY AND CARCINOGENESIS STUDIES AND TOXICITY STUDY

## SODIUM FLUORIDE

V O L U M E 1

P A G E S 1 - 251

At Research Triangle Park, North Carolina.

Thursday, April 26, 1990.

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# A P P E A R A N C E S

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# TABLE OF CONTENTS

## EXAMINATIONS

# TABLE OF CONTENTS

## EXAMINATIONS

The following peer review of draft technical reports of long-term toxicology and carcinogenesis studies and toxicity study of Sodium Fluoride was conducted by the Technical Reports Review Subcommittee and Panel of Experts at the National Institute of Enviromental Health Sciences Conference Center, Research Triangle Park, North Carolina, on Thursday, April 26, 1990, beginning at 8:30 a.m, and was reported by Manie P. Currin, Court Reporter and Notary Public in and for the State of North Carolina.

The following proceedings were had, to wit:

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DR. GALLO: Good morning.

I'd like to get started. We have a very, very full agenda. This is the meeting of the Board of Scientific Counselors and National Toxicology Program. This is the second day of a two-day review, and today is dedicated to the review of the study on sodium fluoride.

Before we get started, Doctor Hart has a few ground rules that he wants to lay out. And then I'd like the Board and the people at the table to introduce themselves starting were Doctor Allaben at the end, but we'll wait until after that.

DR. HART: Well, these are mainly just housekeeping items, but our tentative schedule is sort of a -- well, it's on the sheet, is that we will take the coffee break after the staff and review members make their comments, before the public comments.

I assume everyone knows where the cafeteria is. If you don't, it's down to my left, that direction down there (indicating). If you keep on going you will find it. There are bathrooms down there.

There are also bathrooms up in the -- to my right,

up in that far corner up there.

And there are telephones around the corner over here, in the direction of those bathrooms.

I would emphasize that because of the number of people in the room, that everyone use the mics please, that speaks, at the table or otherwise. A speaker should go to the podium, and -- and use them at all times, because otherwise they won't pick up, and people in the back can't hear you.

Everyone that's in here should be registered, hopefully, or have a badge of some kind.

And finally, and again, tentatively, we will take a lunch break after the public comment period, before the panel resumes its discussions on the report.

And again, there is a cafeteria down there, where you take your coffee break. It will the same one. It will be fairly crowded, I'm sure, and I would just ask you to be patient.

And no food or drink in the conference room, please.

DR. GALLO: I'd like to say this now, and then I'll repeat it again before the public comment. The comment period is seven minutes. And I'm going

-- I'm -- being a lab guy, I've got a lab timer and this is what you're going to hear (sounding timer).

And I'm throwing the hook. I'll let you know when it's six minutes, and that will give you a minute to conclude.

And I would appreciate if you stay to your time. We have a lot of individuals who would like to speak. We have the list closed out, and we have the speakers in the packet in their order of when they asked to speak, so we're going to be going in that order.

And it will be seven minutes and that will give everybody ample time, and it will give the panel members a chance to question, if necessary.

Thank you.

If I could just have the introductions around the table, starting with Doctor Allaben, please.

DR. ALLABEN: I'm Bill Allaben with the FDA and CTR.

DR. BOORMAN: Gary Boorman, NIEHS.

Dr. SILBERGELD: Ellen Silbergeld, University of Maryland.

DR. DAVIS: Harold Davis, School of Aerospace Medicine.

DR. GOODMAN: Jay Goodman, Michigan State University.

DR. HAYDEN: Dave Hayden, University of Minnesota.

DR. GOLD: Lois Gold, University of California, Berkeley.

DR. McKNIGHT: Barbara McKnight, University of Washington.

DR. HASEMAN: Joe Haseman, NIEHS.

DR. EUSTIS: Scott Eustis, NIEHS.

DR. BUCHER: John Bucher, NTP.

DR. GALLO: Mark Gallo, University of Medicine, Piscataway, New Jersey.

DR. GRIESMEMER: I'm Dick Griesemer with NIEHS.

DR. HART: Larry Hart. I'm with the NIEHS, NTP?

DR. RALL: David Rall, NIEHS, NTP.

DR. LONGNECKER: Daniel Longnecker, Dartmouth Medical School.

DR. ASHBY: John Ashby from the Central Toxicology Laboratories at Imperial Chemical Industries in England.

DR. GARMAN: Bob Garman, Consultants in

Veterinary Pathology.

DR. CARLSON: Gary Carlson, Purdue University.

DR. ZEISE: Lauren Zeise, California Department of Health Services.

DR. JOKINEN: Mike Jokinen, NIEHS.

DR. HAARTZ: Janet Haartz, CDC, National Institute for Occupational Safety and Health.

DR. GALLO: Thank you.

I'd like to move right into the program and ask Doctor Bucher to make the presentation on sodium fluoride.

(Doctor Bucher comes to the podium.)

DR. JOHN BUCHER: Thank you, Doctor Gallo.

(Projecting slide one.)

Sodium fluoride is a white, crystalline, water soluble powder. It's one of several fluoride containing compounds that are used in water fluoridation systems and has added to many dental products for the purpose of preventing or reducing dental caries.

Sodium fluoride has also been therapeutically in attempts at treating osteoporosis because of its action to stimulate bone osteoid formation.

The National Toxicology Program has performed

toxicity and carcinogenicity studies with sodium fluoride.

The chemical was administered in the drinking water to F344 rats and B6C3F1 mice of both sexes for periods of fourteen (14) days, six months, or two years.

Fluoride ion is forty-five percent (45%) of the sodium fluoride salt by weight, thus the equivalent fluoride concentrations are about one-half those that I will be giving as sodium fluoride.

In fourteen-day toxicity studies, the sodium fluoride concentrations used ranged as high as eight hundred parts per million (800 ppm) for both rats and mice. The top concentration of eight hundred parts per million (800 ppm) was lethal to male and female rats and to several male mice.

(Projecting slide two.)

Based on the results of the fourteen-day studies, the concentrations chosen for the six-month studies ranged as high as six hundred parts per million (600 ppm) for mice, and three hundred parts per million (30 ppm) for sodium fluoride for rats.

This slide shows the results of the six-month male rat study.

None of the rats died early during the studies, but body weight gain was less in the high dose group.

The teeth of animals given three hundred parts per million (300 ppm) sodium fluoride had a chalky white discoloration, they chipped easily, and they showed unusual wear patterns.

Microscopic sections of incisors that were processed through a typical paraffin embedding step were found less than satisfactory for examination.

These tissues were reembedded in plastic and were resectioned.

This wasn't always successful either, but we were able to examine the incisor teeth of animals from the groups that are indicated here.

A blank indicates that no tissues were examined in this group.

Degeneration of the enamel forming organ was seen microscopically in five of the six high dose animals examined.

Rats also had a diffuse hyperplasia of the glandular stomach in the three hundred -- I'm

sorry, the three hundred and six hundred -- the one hundred and three hundred parts per million (300 ppm) groups.

And one top dose animal had a -- had an ulcer.

Factors that we considered important in the selection of concentrations for the two-year study included the reduced body weight gain, and the ulcer in the animals in the top dose group.

(Projecting slide three.)

The results for female rats in the six-month studies were quite similar to those in male rats.

All of the animals survived to the end of the study. Top dose animals had a lower body weight gain than did the other groups.

The teeth were chalky white and brittle in the three hundred parts per million (300 ppm) dose groups.

But in this case enamel organ degeneration was not seen.

However, the animals did show hyperplasia of the glandular stomach in the one hundred (100) and three hundred parts per million (300 ppm) dose groups and one female rat in the high dose group had a penetrating ulcer.

(Projecting slide four.)

here are the results of the six-month studies for male mice.

Deaths occurred in the top dose group and one male mouse given three hundred parts per million (300 ppm) also died during the studies -- before the end of the studies.

Body weight gains appeared reduced in animals given two hundred parts per million (200 ppm) in higher doses. The teeth of mice receiving one hundred parts per million (100 ppm) in higher concentrations were chalky white and they chipped easily.

Degeneration of the enamel forming organ was also seen at the two highest doses, as we see here.

And there was an evidence of an increase in bone osteoid in animals given fifty parts per million (50 ppm) and higher concentrations in the study.

Lesions were also observed in the kidney, the liver, and the myocardium in animals that died early, before the end of the study.

The factors in this study that we considered important in selection of doses for the two-year

study included the reduction in body weight gain, in two hundred parts per million (200 ppm) and higher, and the deaths of animals at six hundred (600) and three hundred parts per million (300 ppm).

(Projecting slide five.)

The results of the six-month study in female mice were very similar to those of the males. There were deaths observed at six hundred parts per million (600 ppm) dose group.

Mean body weight was less in animals given two hundred parts per million (200 ppm+) and higher in the water.

The tooth -- the gross appearance of the teeth was quite similar to those in the male mice at the same concentrations. The same kind of discolorations and chipping were observed.

We noted degeneration of the enamel forming organ in the three hundred (300) and six hundred parts per million (600 ppm) dose group.

There was increased osteoid formation in the femur in mice given one hundred parts per million (100 ppm) and higher concentrations.

And, again, the mice that died early showed

lesions in the kidney, the liver and myocardium.

(Projecting slide six.)

To move on to the design of the two-year studies, the animals used again were the F344 rat and the B6C3F1 mouse.

The concentrations chosen for the drinking water in the two-year studies were zero, twenty-five (25), one hundred (100), or a hundred seventy-five parts per million (175 ppm) of sodium fluoride, which is equivalent to zero, eleven (11), forty-five (45), or seventy-nine parts per million (79 ppm) fluoride ion.

Higher concentrations than the hundred seventy-five parts per million (175 ppm) were not chosen to prevent the decreased weight gains seen in rats given three hundred parts per million (300 ppm) and mice given two hundred parts per million (200 ppm) in higher concentrations in the six-month studies, and to prevent the occurrence of ulcers which occurred in rats given three hundred parts per million (300 ppm) sodium fluoride.

It should also be noted that a previous two-year study that used a top concentration of a hundred parts per million (100 ppm) did not show

any significant toxic effects in rats or mice, thus it was deemed appropriate to increase the top concentration to a hundred and seventy-five parts per million (175 ppm) for the study -- for the study which is the subject of this report.

For the two-year study, the base group sizes were eighty (80) in controls, sixty (60) in low dose, fifty (50) in mid dose, and eighty (80) in high dose.

Groups of ten additional animals were killed at each of the dose groups at six months and fifteen (15) months, and here is the total number of animals in the study per section and species.

Now, to help put these doses of sodium fluoride that we've used in this study into some kind of perspective, the optimal levels of fluoride ion in public water supplies are considered to be about one part per million (1 ppm), and the current EPA recommended upper limit on fluoride occurring naturally in water supplies is four parts per million (4 ppm).

These concentrations compared directly to the eleven (11), forty-five (45) or seventy-nine parts per million (79 ppm) of fluoride ion that we've

used in the water in the study.

The mice and rats drink more water proportionate to body weight than do humans, and rodent diets routinely contain higher amounts of fluoride than does the human diet, thus the actual doses that are achieved in the rodents are higher in comparison to the typical human exposure than would be predicted based solely on a comparison of the concentrations in the drinking water.

(Projecting slide seven.)

In this slide, you can see estimates of total fluoride, and I want to emphasize this is total fluoride not sodium fluoride.

The fluroide intake from the diet and the water and in the control and dosed rats and mice in this study, and also in animals that comprise our historical data base.

These numbers are rough estimates and they're based on several assumptions. We've determined that our typical NIH-07 diet contains from about twenty-five (25) to as much as fifty parts per million (50 ppm) of fluoride.

Most of this fluoride is contained in the fishmeal component in the diet, and as a

containment of calcium and other mineral additives.

As part of the sodium fluoride studies, we've made a rough estimate of the fraction of dietary fluoride that is actually absorbed by the animal, and we have determined this to be about sixty percent (60%).

The diet that we have used in the two-year sodium fluoride study used selected lots of fishmeal and mineral salts that were low in fluoride, and we were thus able to lower the background fluoride exposure from the diet to the animals.

The diet that we used in this study averaged just under eight parts per million (8 ppm) fluoride.

So, that the numbers that you see on this slide take all these factors into consideration.

The fluoride intake of the control group is contributed entirely by the diet. The animal -- the water that these animals drank was deionized and contains less than point one part per million (.1 ppm) fluoride.

The amounts of fluoride given to the other groups reflect fluoride contributed by both the

diet, which is this portion, right here (indicating), and that in the drinking water.

The total intake of mice is higher than that for rats, because they eat and drink more in proportion to body weight than do rats.

You can also see from this slide, that animals with previous studies, and control groups where fluoride has not been closely controlled in the diets may have been receiving fluoride in excess of what the low-dose animals in this study were receiving.

(Projecting slide eight.)

As a consequence of ingesting the fluoride doses that were given on the last slide, fluoride accumulated in the bones of rats and mice at the levels shown in this slide.

Although it took fairly high daily doses to get the fluoride concentrations in bones to these levels, these concentrations are similar to those reported -- reported in the bones of humans who've had varying exposures to fluoride.

For example, it's not uncommon for ashed bone samples of normal subjects living in fluoridated areas to approach a thousand parts per million

(1000 ppm) fluoride.

Fluoride levels of five to six thousand parts per million (6000 ppm) or higher values have been reported for people living in areas with drinking water that exceeds four parts per million (4 ppm) fluoride, or who are taking sodium fluoride for treatment of osteoporosis.

During the two-year study, mean body weights of dosed and control groups of rats and mice did not differ from controls. Here are the body weight curves for rats (indicating), male rats on the top, female rats are on the bottom.

And these curves -- weight curves are quite similar to those that we typically see in other studies.

(Projecting slide ten.)

These are the weight curves for mice. Again, male mice are on the top, female mice are on the bottom there (indicating).

This does not appear to be an effect of the sodium fluoride of administration on the body weight, but the maximum average body weights that were attained were higher by as much as twenty percent (20%) for males, and as much as thirty-five

percent (35%) for females than the average maximum body weights that had been obtained traditionally in our historical control groups of animals.

The reason for this increased weight gain in this study is probably related to factors that are associated with a program wide change and the way we have housed our animals which took effect shortly before this study began.

The -- the weights obtained by historical control mice are for animals that were group housed five per cage.

In the sodium fluoride studies, and other mor recent studies, we have changed to housing mice individually.

As a consequences of this change, we're seeing an increase in body weight and an apparently concomitant increase in the incidence of liver tumors in male and female mice.

An association between increased liver tumors and increased body weight has previously been reported by Doctors Haseman, Rao, and others in retrospective analyses of our data base.

(Projecting slide eleven.)

This slide is from a report that's in

preparation by Doctors Haseman and Rao and others.

And while all other contributing variables have not yet been ruled out, it does show clearly a relationship between maximum weekly average body weight, and the liver tumor rates in control group -- control animals from our historical data base.

These data include the results from some studies that have not yet been through per review. Thus, those studies are not reflected in the historical control information that -- that is given in the sodium fluoride report.

(Projectint slide twelve.)

The survival of dosed and control animals in the sodium fluoride studies was good, and was not affected by the administration of the chemical.

These are the curves -- the survival curves for rats, again male rats are on the top, female rats are on the bottom. (Indicating)

(Projecting slide thirteen.)

And these are the survival curves for mice (indicating), male mice on the top, female mice on the bottom.

Note that the scale here is cut off.

(Projecting slide fourteen.)

During the two-year study the teeth of rats developed dose-dependent incidence of whitish discoloration and mottling, and rats, primarily males, had an increased incidence of tooth deformities and attrition.

You see the numbers up here. These are percentage in the animals that would be various lesions.

Microscopically, the teeth of dosed male and to a lesser degree, female rats had increased in the diagnosis of dentine dysplasia and degeneration of ameloblasts.

(Projectint slide fifteen.)

The whitish discoloration and mottling of teeth was also observed in the two-year mouse studies, but in this case attrition appeared to be much less severe than in the rats.

And there was an increase, although this was a statistically significant increase in dentine dysplasia in male mice, this was not -- an increase in this lesion was not seen in female mice, but the background incidence of this lesion in mice increased dramatically during the two-year study, so it makes it difficult to discern a treatment

related effect on dentine dysplasia in mice.

(Projecting slide sixteen.)

The only nonneoplastic bone lesion that appeared related to sodium fluoride administration was an increase in the incidence of osteosclerosis in female rats.

The more severe cases of osteosclerosis occurred in high dose female rats. These lesions were visible on radiographs.

No other nonneoplastic lesions appeared related to chemical administration in rats or in mice.

(Projecting slide sixteen A.))

There were differences in the incidences of neoplasms between dosed and control animals at a number of tissue sites in these studies.

We've examined in detail tumors of the oral cavity, thyroid gland, and skin of rats, and of the hematopoietic system in mice and have concluded that there is insufficient evidence to consdier the small increases in certain tumors in these organs as possibly related to sodium fluoride administration.

There were also decreases in the incidences of

uterine stromal polyps in rats, and neoplasms of the harderian gland and pituitary gland in mice.

We've also examined these tumor sites and have concluded that it is unlikely that the decreased incidences are related to the sodium fluoride administration, but the effect in the uterus was one of the stronger effects statistically seen in the study.

The only other neoplasm that we believe warrants consideration is osteosarcomas in male rats.

(Projecting slide seventeen.)

As you can see in this slide, a small number of osteosarcomas of bone occurred only in the mid and high dose groups of rats, male rats. They occurred with a statistically significant dose response trend. This is the number right here (indicating).

Three of these tumors occurred in the vertebra, and one was a microscopic tumor found in the humerus. An additional extraskeletal osteosarcoma was also found in a -- in a fourth high dose animal. This tumor was determined to originate in the subcutaneous tissue.

There are a number of factors that enter into the determination of whether this is a true chemically related effect or whether this incidence likely occurred by chance.

I'd like to briefly review some of these major points to help set the stage for further discussions.

(Projecting slide eighteen.)

There were several differences in the protocol used in the sodium fluoride studies when compared to the protocols that had been used to study other chemicals in the program.

We've examined histologic sections of bone from the tibia, femur, humerus, thoracic vertebra, maxilla, incisive bones, nasal bones, and the mandible in this study, plus any grossly observed bone lesion was also cut in.

In a typical study we routinely take sections of bone from the maxilla and the rib, or the femur, in addition to any grossly observed bone lesions.

We also took whole body radiographs of all animals in this study to assure that any grossly visible lesions were not missed by the prosectors.

The important point is that dosed and control

animals received an equivalent examination of -- of -- in all respects including the evaluation for bone lesions, and that the evaluation was somewhat more extensive in the sodium fluoride studies than in typical studies.

(Projecting slide nineteen.)

Other factors that we feel are important in the consideration of this lesion pertain to the use of the historical control data from previous studies.

We maintain a data base of the incidences of all tumors that occur in control animals in our studies, and we find this information is helpful in the analysis of tumor incidences that are found individual studies.

Historically, osteosarcomas have occurred with an incidence of about zero point six percent (0.6%) in control male rats.

Two subcutaneous neoplasms have appeared in previous studies. These were coded as subcutaneous neoplasms, but we have no way of telling at this time if these osteosarcomas represent primary tumors that resulted from the ossification of a sarcoma in the subcutaneous tissue, or if they

arose as a metastatic bone neoplasm.

But overall, most of the osteosarcomas that have occurred in our studies were found in bone and these were in control groups, and they were found on gross examination late in the two-year studies.

About twenty percent (20%) of the osteosarcomas in bone typically occur in the vertebra. Another twenty percent (20%) are found in the skull and about ten percent (10%) of the osteosarcomas that we've seen have been found in the rib, with the rest being scattered among the long bones, pelvis, and also a couple were -- as I noted, were found in subcutaneous tissue, and some were found in the lung.

The occurrence of an incidence of zero, one, two, or three neoplasms in any one control group fits a Poisson distribution in our studies.

This distribution, the Poisson distribution would predict that we would see by chance an incidence of three osteosarcomas once in the hundred and twenty-two (122) studies in our data base.

And, in fact, one of the previous studies, we have seen as many as as three bone osteosarcomas in

a group of fifty male rats.

This incidence of six percent is higher than the incidence of osteosarcomas seen in the high dose group in the sodium fluoride studies.

And one final point that's important in the -- concerning the use of historical control data that I mentioned previously, is that the fluoride content of diet was not monitored or controlled in previous studies.

It likely always contained more fluoride than we used in the studies -- in the current study.

(Projecting slide twenty.)

Other factors that we feel are important involve more scientific questions.

For example, it would be reasonable to expect a neoplastic response if one were to occur in an organ that accumulates fluoride, and we have shown an accumulation of fluoride in the bones in the animals in this study, but the fluoride levels in bones in high dose males rats did not differ from those in the high dose female rats or male and female mice.

And there was no osteosarcoma response in these groups.

Fluoride is not thought to accumulate in soft tissue to any significant degree, and it's questionable whether it's appropriate to combine the subcutaneous osteosarcoma with the bone osteosarcomas for statistical analysis.

There are two reasons for this. The first relates to the differences in the accumulation of fluoride at the site of origin of the tumor, which I've just mentioned, and the second relates to the different cell of origin, or target cell.

Bone osteosarcomas are thought to result from neoplastic transformation of osteoblasts of bone, and these tumors can metastisize to soft tissues.

On the other hand, sarcomas of soft tissues can occasionally produce osteoid resulting in a tumor that is classified as an osteosarcoma.

But the tumors that originate as soft tissue sarcomas are not primary bone tumors.

Most chemically induced neoplasms in bone are thought to occur in long bones.

In our study, three of the four osteosarcomas in males rats occurred in the vertebra. On the other hand, it would appear that sodium fluoride is genotoxic in a number of genetic toxicity assays,

through as yet undetermined mechanisms. So, a neoplastic effect in a tissue that accumulates fluoride would appear possible.

(Projecting slide twenty-one.)

After carefully weighing these and other factors that are discussed in the report, we have concluded that the evidence is weakly supportive of an association between osteosarcomas and the administration of sodium fluoride to male rats.

We feel, however, that the evidence is inconclusive, and believe it is best described by, or best fits in, our classification system in the equivocal evidence category.

And this category is defined as a marginal increase in neoplasms that may be chemically related.

Thus to summarize, there was -- under the conditions of these studies, there was equivocal evidence of carcinogenic activity in male rats, based on osteosarcomas of the bone.

There was no evidence of carcinogenic activity in female rats or in male or female mice, and we also observed evidence of dental lesions typical of fluorosis in rats and we saw an increase in

osteosclerosis in female rats.

There is one other thing that I'd like to mention, and this concerns the liver tumors that I mentioned earlier in female -- in male and female mice.

As I said earlier we had a high incidence of hepatocellular adenomas and carcinomas in both dosed and control groups of male and female mice.

Occasionally, phenotypic variants of hepatocellular carcinoma, such as hepatocholangiocarcinoma, or hepatoblastomas will occur within an existing neoplasm.

Several of these variants were diagnosed in male and female mice, and were combined for purposes of analysis with the hepatocellular carcinomas.

During the pathology review procedures several of the tumors diagnosed originally as hepatocholangiocarcinomas were considered more appropriately called hepatoblastomas.

The diagnoses were changed under "liver" in the incidence tables in the report that you have, but we neglected to change the diagnoss under all

organs where metastases appeared for some of the animals.

This is one of a number of minor corrections to the report that will be made in the next draft.

Now, with that I'd like to conclude and turn the podium over to Doctor Eustis, who will describe some of the histopathologic features of selected lesions seen in sodium fluoride studies.

DR. GALLO: Thank you, John.

Doctor Eustis?

(Doctor Eustis comes to podium.)

DR. SCOTT EUSTIS: Thank you.

As Doctor Bucher has indicated, one of the principal effects associated with the administration of sodium fluoride to rats involves the incisor teeth.

As most of you know, the incisor teeth grow continuously throughout the lifetime of a rat. Therefore, all tissue components that give rise to the tooth structure can be observed at any time.

Furthermore, toxic effects associated with tooth development will also be seen in the incisor teeth throughout their lifetime.

This is not true for the molar teeth which do

not continuously grow.

(Projecting slide.)

This slide shows cross-section of the incisor tooth, near the apical end embedded in the bone.

This portion of the tooth is the pulp, this is the dentine layer, and this is the layer of enamel.

Beneath the layer of the enamel is the layer of immunoblast which secrete the enamel.

The effects of fluoride on the immunoblast have been well characterized and previously reported in the scientific literature. There is degeneration in necrosis of these cells, primarily in the late secretory and maturation stages.

It is important to note that this degenerative -- that this is a degenerative process and is not considered a preneoplastic lesion.

The other effect of fluoride that can be seen in this slide is the malformation of the dentine layer that is seen here (indicating). This is the lesion that was diagnosed as dentine dysplasia. The dentine layer should be a uniform, even layer, and you can see that it is malformed and misshapened.

He have also observed an increased incidence of osteosclerosis in female rats after receiving sodium fluoride.

Osteosclerosis is a spontaneous disease of uncertain pathogenesis seen primarily in aging female rats.

This is a cross-section of a femur with the cortical bone of the diaphysis, and this is the marrow cavity.

Normally, the marrow cavity is filled with adipose cells, hematopoietic cells, and a huge specular of bone.

In this femur the marrow cavity is filled predominantly with cancellous bone.

As Doctor Bucher mentioned, there were three osteosarcomas of bone in the one hundred and seventy-five parts per million (175 ppm) dose group of male rats, and one in the one hundred parts per million (100 ppm).

An extraskeletal osteosarcoma arising in the subcutaneous tissue was observed in a fourth high dose male rat.

All were seen radiographically except for very early neoplasms found within the medullary cavity

of the humerus of one.

This is a lateral view of the radiograph showing one of the vertebral osteosarcomas. The osteosarcoma is located here surrounding the coccygeal vertebrae.

(Projecting slide.)

this next slide is a histologic section from the vertebral osteosarcoma showing the abundant osteoid production which characterizes this neoplasm as an osteoid sarcoma.

(Projecting slide.)

This next slide is a lateral view of the radiograph showing the subcutaneous osteosarcoma. It is this large rounded mass in the subcutaneous tissue here.

This is the femur of the hind leg.

There is clearly no association with the bone and no evidence of a primary bone neoplasm.

This conclusion is a critical point in the evaluation of the significance of these neoplasms.

In contrast to the abundant osteoid production seen in the vertebral osteosarcoma, the subcutaneous neoplasm contains a more heterogenous population of cells with very little osteoid

production which is this pink material, and some indications of cartilage differentiation, which is the more pale appearing material.

Finally, we have received some comments indicating confusion about the evaluation of hepatocellular carcinoma, the hepatoblastoma, and hepatocholangiocarcinoma in mice.

Hepatocellular carcinomas are malignant neoplasms with a heterogeneous population of cells.

These phenotypic differences are a reflection of the anaplastic and malignant nature of any malignant neoplasm.

In this slide you can clearly see two populations of neoplastic hepatocytes within this one tumor, with different growth patterns.

This is a trabecular pattern with small cells. This is a more solid growth pattern over here (indicating with pointer).

This is another hepatocellular carcinoma with a different phenotype and growth pattern.

The growth pattern here is more glandular, and the cells appear even less like normal hepatocytes.

Occasionally, hepatocellular carcinoma may contain proliferating bile ducts as shown in this

slide.

These are bile ducts (indicating).

If the proliferating bile ducts are in sufficient number and there are sufficient indication that they are a primary component of the neoplasm, a diagnosis of hepatocholangiocarcinoma is made.

Finally, some hepatocellular carcinomas contain populations of cells that resemble fetal liver cells, and the neoplasm is called an hepatoblastoma.

This was a large neoplasm about two centimeters (2 cm) in diameter. This is the component that looks like typical hepatocytes, and this is the component that resembles the fetal liver cells.

It is important to note that these are all hepatocellular neoplasms, and when they are evaluated, they are combined with the other hepatocellular tumors. We feel there is no sound biological reason to evaluate them individually.

There was no increase in the hepatocellular neoplasms in rats or mice receiving sodium fluoride.

That concludes our slide presentation.

DR. GALLO: Thank you, Scott.

I'll take comments in the reverse order that they are in the schedule.

Doctor Longnecker.

DR. LONGNECKER: This is a well written report and I believe reflects a carefully done study.

I was satisfied with the background literature. It's fairly reviewed and referenced, but I recommend that the staff review the documents that have been submitted and add any significant information that is helpful.

The design of the two-year study was standard with certain features that apply -- imply extra care such as the inclusion of a group of control rats to allow age matched controls for early deaths and sacrifices in the treated groups.

The dose group is clearly appropriate, and I believe that the levels of dosing yielded clear evidence of biologic effects without significant decrease in animal growth.

The photomicrographs are good quality and support the diagnoses that have been given.

The -- there were neoplastic lesions in

several tissues as have been reviewed by Doctor Bucher, but I agree that only the osteogenic sarcomas stand out when one considers all the observations and historical control data.

For the reasons that he has reviewed, there is a suggestion of a potential mechanism that supports the possible significance of these lesions.

Ultimately, I agree that the best interpretation is that the data is inconclusive and classified as equivocal.

DR. GALLO: Thank you.

I believe Doctor Ashby is next.

DR. JOHN ASHBY: This report is technical report number three hundred and ninety-three (393) of the NTP. And this means that the NTP have now evaluated possible carcinogenicity of nearly four hundred (400) chemicals.

Now, I have read every one of those reports. This one is most thorough and detailed study reported to date.

The report is longer than usual, but this reflects the importance of the chemical, and every aspect of the data has been carefully considered in this report.

Now, it is a long report, and I spent a lot of time working on it, and I found very few points that I wish to raise now with the NTP scientists.

Before I start with those -- with those points I'm going to raise into context, I'd like to give my initial conclusion before I start, and that is that I agree with the essence of the report's conclusions and these are most adequately summarized in the report around page ninety (90) -- ninety-one (91). I'd just like to read those so you know where I stand.

"Taken together the current findings are inconclusive but are weakly supportive of an association between sodium fluoride administration and the occurence of the osteosarcomas in male rats.

No compound related increases in tumor incidences were observed in female rats, or in either sex of mice."

And my comments lead actually up to that conclusion, again.

I want to raise six topics that I think may be important for us to discuss or to be aware of. Some have already been raised, of course.

First of all, briefly the genetic toxicology of -- sodium fluoride, fluoride iom, of course, will not bind to DNA. And consistent with that, this chemical is negative in many studies, and in some of them assays prove same.

And when you move into coach mamallian cells or other systems, nonbacterial systems, in vitro, as in petri dishes, in vitro, there is evidence of genetic changes being produced.

They are curious. They are not what we normally consider to be routine genetic changes. There are several aspects that are interesting.

First of all, there seems to be a threshold at this level; in other words, there are doses where nothing happens, and then as you increase the dose you get to a point where you start seeing effects. Most of the effect studies have been chromosomal elaborations.

The second point is that we really are completely lost for a mechanism of action of this. It fits into no standard understanding of how a chemical might cause mutations or genetic damage.

There are several possible ideas that are raised in the report and in other people's papers.

One of them is that fluoride is known to affect enzymes, and it can hydrogen bomb to key science on enzymes and maybe even deinactivate them.

And it's possible that fluoride at some certain critical dose levels is affecting enzymes associated with the maintenance of DNA.

Another thing that really needs to be considered is that calcium atoms are critical in the normal controlled cells, and fluoride will precipitate calcium atoms such as in soluble calcium fluoride, and that can have genetic effects.

So, really, loss for a mechanism of action, but these effects are there <u>in vitro</u> in mammalian cells, and they're speaking of a totally normal mechanism, and that means we cannot extrapolate those effects with equal confidence as we could the standard carcinogens.

And the third point is, of course, that many chemicals show genetic changes in cold petri dishes and then proceed to do nothing in animals, neither produce cancer nor genetic changes.

And so having genetic effects <u>in vitro</u> is an indication of concern, but it is not definitive

of anything.

And when we come to in vivo experiments where the chemical has been dosed to rodents and genetic changes have been monitored in vivo, there is no reproducive evidence of a genetic effect in animals.

There are some reports of positive responses, and in an equal number, if not more, have negative responses.

But one of the key things in science is the effects that you're talking about should be reproducible and the effects we see in the literature in rodents, genetic effects, are not reproduceible, and reproducibility is a key aspect of good science.

And the re- -- the recent debate about cold nuclear fusion illustrates that well.

I do not consider that -- in summarizing this genetic toxicology, I do not consider the report of genotoxicity as sodium fluoride has bearings on the tumors that we're discussing today.

That's a personal opinion, of course.

Second point is the expectation of carcinogencity before the study was done.

There is no evidence from standard cancer studies in rodents that sodium fluoride is a significant carcinogen, within the context of the detailed, multiple cancer bioassays that we consider nowadays such as this one here.

All previous reports are inadequate within the context of the present study which is representative of what cancer bioassays now are.

So, there is really no previous art to indicate the carcinogenic effect. And the sodium fluroride itself makes life pretty simple because it's not metabolized. And one of the most -- the great complicating factors of creating chemical carcinogenicity is anticipating metabolism.

But fluoride is not metabolized, so it's either going to do something, or it's not going to do anything, so that simplifies the prediction.

From what we've heard already, if it was going to be a carcinogen, it is unlikely that there would be any sex or species differences, because those differences are usually a reflection of metabolic differences between sexes and species.

And although we are thinking about brain tumors at one point, I'd like -- just like to bring

you two parts from the report that I think are particularly relevant.

Given the propensity of fluoride to accumulate in bone and tissue must be the most likely work for carcinogenic effect to be seen.

The high -- high levels of fluoride did accumulate in the bone of animals in all the four test groups.

And the statement on page ninety-one (91) of the report that, "High dose female rats have the clearest evidence -- have clear evidence of fluoride induced osteo- -- osteosclerosis", means the females rats which didn't come to tumors at all clearly were showing the effects of fluoride accumulation and had an increase in bone tumors was only recorded in the male rats.

Thus, the fact that this report centers on osteosarcomas is appropriate, yet the statement, again, taken from the report that fluoride was found to accumulate in the bone of the female rats, and male and female mice to a similar extent as in male rats, I suggest that we should really be quite cautious in drawing causative associations.

So, the expectation, to summarize that, is

really not high that it would be a carcinogenic. If it was going to be one it should be -- it should be equally active in both sexes in both species, I think.

And the bone is a target that you would obviously pay most attention to.

Just very briefly, a third point on the setting of dose levels, it ob- -- obviously, it's a critical aspect of the bioassay that the animals have received a sufficient dose level, and it's normal practice to -- to give the maximum tolerated dose.

This is a very delicate balance in trying to set the maximum tolerated dose. It's a balance between animals dying due to toxicity or animals receiving the maximum tolerated dose and living.

These dose levels were selected by standard NTP methods. There actually was no effect on the rodent body weights, but equally the survival was very good, and so as far as practical, the dose selected -- the doses selected were the maximum achievable.

For those of you who were here yesterday, we

had a case of sodium azide where the same selection criteria we used in that compound proved to bemuch more toxic than anticipated. And there were a lot deaths.

And so this is a very delicate balance. And I think a balance was struck well in this study.

Fourth point, the actual rat bone tumors, osteosarcomas in the male rats only.

Without repeating what's been said before, I'll just make the two points that I want to make about this.

First of all, the effects, you remember, were naught out of eighty, naught out of fifty, one out of fifty and then three out of fifty.

There was such a weak effect, two criteria are used routinely by the NTP to determine if a biologically significant effect has been induced, and these are statistical analyses in reference to the radius or otherwise to the tumors, i.e., use of historical data base from the earlier three hundred and fifty (350) reports.

And incidentally, access to such a large number of similarly conducted studies, that's one of the unique strengths of the NTP and its analysis

at consummation.

If we look at the first one, statistic analysis, these data are at the very limits of statistical analysis you will see if you read the report.

No individual dose gave a statistically significant increase in bone tumors viewed together, in other words as a trend, there was a statistically significant effect.

As a matter of fact, it was about three chances in a hundred that that trend was there by chance, at P027.

So, in any one test group, one cannot be sure that certain fluoride induced bone tumors, but the overall impression, in all in- -- all doses was that it may have. That's a summary of what you have.

And that means the effect is equivocal.

That's what statistical analysis says, when you look at the historical control data base and there are -- there are problems, as you've heard, the tumors are very rare in earlier studies, six in a thousand in male rats and two in a thousand thousand in female rats.

And the highest number ever seen, three out of fifty (50) is higher than in the present high dose study -- high does of this study.

But the report authors warn against the use of historical control data base in this report very clearly for the two reasons you've heard.

First of all, the fluoride levels in the diet weren't as stringently controlled earlier, and so thus historical controls may actually be part of a cander bioassay which was conducted in between the low and the medium dose in the present study. That is complicating factor.

And secondly the second portion they give, is that given that the bone was a possible target tissue, the pathologists extended their microscopic assessment of bone tissue in the present study to a different site where in earlier ones they'd only evaluated two tissue, two bones microscopically.

And this could have skewed the historical data base.

And you remember that one of the three tumors in the high dose was actually a microscopic tumor, and that's one in three which is a critical component of this analysis, and we really have no

adequate historical data base of microscopic analysis.

So, given those given the two problems, the fluoride in the diet, and the limited historical microscopic anal- -- analysis, we cannot rely on historical data base as much as we normally would, So we're back to the present eighty control animals, and that's what the authors advise us to do and the statistical analysis with present data, and that gives an equivocal response.

Fifth point, are the other possible sites of carcinogenesis. I don't think I'll actually go over these. I was not concerned about any of them.

There were thyroid effects in the male rats, and I think the authors' reports have completely convinced me that those are not significant effects.

Likewise, with the lymphomas in mice, the historical data base extends from ten to seventy-four percent (74%) of the control animals having that tumor type, and the authors conclude there is no effect.

And again, the mouse liver, there was no effect, and of course, those of you who know these

reports will realize that the mouse liver is the most sensitive indicator of carcinogenicity, is by far the major site of chemically induced cancer, and no effects were observed in the present study.

The last site of carcinogenesis was the subcutaneous tumors of the oral mucosa.

And those -- those are worth the most attention, but again, I'm satisfied with the handling of them in the report. It was a marginal effect; it was not statistically significant; the tumors were present in the -- in the control animals, and probably most important, there was no preneoplastic hyperplasia.

And previous studies have put a relationship between preneoplastic changes and the eventual appearance of tumors and there was no such effect in this study.

The NTP pathologists conclude that no chemical induced effects were seen in this tissue.

I tend to agree with them, but I'm sure we'll discuss it more later on.

And then finally, my conclusion is just really to repeat the two phrases I said before which are

already in the report.

Taken together the current finding are inconclusive but are weakly supportive of an association between the sodium fluoride administration and the occurrence of osteosarcomas in male rats, no compound related increases in tumor incidences were observed in female rats or either sex of mice.

DR. GALLO: Thank you, John.

Just one other comment on the historical control data.

It should be noted that with the exception of the first fluoride study, this is, I believe I'm correct, the first study where radiographs were done routinely. So that also supports your point that we have to use current control.

Thank you.

Doctor Garman?

DR. ROBERT GARMAN: Thank you.

I have no additional criticisms of either the overall report or its conclusions.

The studies encompassed by this report were well designed and appeared to have been thorough -- thoroughly con ıcted.

In the discussion section, a very conscientious attempt is made to scientifically analyze all the possible links between the development of a small number of osteogenic sarcomas in the male rats and the levels of fluoride in their drinking water.

We would, I'm sure, all agree that the small numbers of osteogenic sarcomas seen in the high dose male rats would have been totally discounted as being treatment related, were it not for the factthat fluoride both localizes in bone and has known effects upon bone osteogenesis.

The NTP scientists have certainly made no attempt to discount these tumors. Instead, every possible argument of logic and accepted statistical test has been applied to these tumors data in an attempt to test the scientific hypothesis that they might be treatment related.

I sincerely believe that the only conclusion that one can reasonably reach is that these osteosarcomas may or may not have been related to the high levels of fluoride in the drinking water.

In other words, a level of evidence of equivocal for the male rat.

One of the NTP's most vital roles is to conduct chronic bioassays such as the sodium fluoride study in order to obtain data which might be predictive of human risk.

In doing so, the program scientists are often caught between those critics who feel that information obtained from rodent studies have no application to man, and those who would take small increases in tumor frequencies which could represent random occurrences and who would interpret these small increases as representing significant risks to the human population.

Those who would wish to make inferences on human risks based on the small number of osteogenic sarcomas seen in male rats, consuming sufficient sodium fluroide to induce clinical fluorosis, for those that who would do that as well as for the NTP scientists who I believe are contemplating future studies on fluoride and rodents, I have one further suggestion.

Because we are dealing in these rodent studies with levels of fluoride in the water which might be expected to induce increased bone fragility, and because there is at least some

evidence that fracture formation and subsequent bone healing may be associated with a slightly increased incidence of osteogenic sarcoma in humans and other animals it might be possible that the increased numbers of osteogenic sarcomas, if they are treatment related, might be a manifestation not of a carcinogenic effect of fluoride at all, but rather a possibly -- a possible result of increased bone remodeling related to the normal bone healing process.

The female rats may not have the same degree of bone fragility as the males because of the increased frequency of osteosclerosis seen in this sex. The mice may not have because of differences in bone mass to soft tissue mass.

My point is that in future studies, if these are conducted in rodents, one might wish to include measurements of bone tensile strength in relationship to the levels of consumed fluoride.

If a possible connection between bone fragility and bone tumor development could be substantiated, this might alleviate some of the public's concerns about consumption of low levels of fluoride in either the food or water which would

be significantly below those expected to result in clinical fluorosis.

In conclusion, I would like to commend the NTP staff scientists for the excellent job which they have performed in collecting, collating, and interpreting these data. That the results of the study are equivocal for one rodent sex and species, is, I believe, only an indication of the fact that it's an imperfect world, and that the response of biological systems are often unpredictable.

Certainly additional research in this area needs to be performed. And it is both hoped and anticipated that in the not too distance -- distant future, we will be able to discuss mechanisms of cancer induction, and that there may come to be a realization that depending on the underlying mechanism, there may be a threshold exposure below which there may be no increased cancer risks for the human population.

My only suggestion with regard to the report would be with regard to the description of the pathology quality assurance and PWG process. While I was very happy with that section myself, I have come to realize that that should be "beefed" up a

little bit, particularly with regard to the mouse liver tumors, and elaborated discussion on the subjectivity of histopathologic diagnosis, the importance of consensus opinion, and the numbers of diagnoses, perhaps that were changed, and a little bit more information, since this report is going to be so heavily scrutinized.

Thank you.

DR. GALLO: Thanks Doctor Garman.

It does my heart good to hear the word "mechanism" come from different places on the table all of a sudden.

What I'd like to do now is open it up to the Panel and wherever you want to start.

Doctor Allaben, any comments at all?

DR. ALLABEN: I'd like to essentially echo what's already been said.

I think it's a very well conducted study. It has no -- no flaws that would make the interpretation of the study any different than the program has.

DR. GALLO: Thank you.

Doctor Silbergeld?

DR. ELLEN SILBERGELD: Thank you very much.

I also concur with many of the statements that have been made as well as the text of the report.

I'd also like to note that this report in many ways vindicates the whole undertaking of the National Toxicology Program, and the cautious and careful use of experimental data in providing preliminary information for use in many different arenas.

I think it's important to emphasize that the purpose of these NTP studies fulfills only the initial phase of the very involved and complex process known as risk assessment and risk management in this country, and that the purpose of these studies is, in fact, to provide information going towards the identification of a hazard.

It is not information that goes beyond that step in risk assessment, and should not be over interpreted to provide that kind of information.

In addition, although as you noted, Doctor Gallo, we have discussed the issue of mechanism, these studies by their design do not generally provide definitive information on mechanism although they can suggest directions for further mechanistic based research.

Some of these may be apparent in the study, and some of these may be useful to note at this point. I would underline very strongly the recommendations that Doctor Ashby made for further work in terms of potential genotoxic or gene compound interactions between fluoride and genetic material and the regulation of gene expression as it may be involved in any of the pathophysiology of this compound.

I would like to speak to the issue of the observations of restricted findings in one sex one species. It's noted that the effects observed in bone tissue insofar as those can be interpreted with the present data base appear to have occurred only in the male rat and not in the female rat and nor in either sex of mice.

There may be some biologic reason to expect a difference in bone response, although as Doctor Ashby points out, our considerations in this arena are probably very simple compared to many more complex mole- -- molecules that undergo metabolic transformation which may be expected to be influenced by species and sex.

There are, in fact, considerable differences

between males and females in terms of bone physiology, both in terms of development, maturation, and synescence.

And it may be the case that the signal of osteosclerosis observed in the females represents there are sex related differences that may have some implications for other pathophysiologic responses of this tissue.

We do not, I presume, know exactly where fluoride is going in bone. Although it is clearly associated with the mineralized phase.

And the hypertrophy of the mineralized phase in osteosclerosis may represent the sequestration that is not without pathologic consequence, but it may, in fact, reduce the possibility of osteosarcoma formation.

It's something that could be examined on a microscopic bases, as well as, a physiologic basis.

I did note that, in fact, in, I believe most cases, the females of both species did accumulate more fluoride in bone as compared to the male and that may again, reflect a different compartmentation, which may -- which may to a certain extent have provided some protection

against the induction of sarcoma, if, in fact, a statistically significant induction is observed in the male.

At any rate that may also speak to mechanism as well as possible differences in response based on those species and on sex.

I would note another concern which is that in terms of the dosing, there are two aspects to be kept in mind.

One is, of course, as Doctor Ashby pointed out, it is customary to design in these chronic studies doses close to the maximum tolerated dose, in order to construct a design which permits us the examination of the maximum number of animals surviving to the end of the study, but at the same time is clearly within the range that is producing a physiologic response in the subject.

And I agree that this study seems to have balanced those two factors well.

However, it is important to note that the dose range is not, as is sometimes the case, orders of magnitude higher than that encountered in human population, nor is the body burden expressed as concentrations in bone orders of magnitude higher

than that found in human populations also ingesting fluoride.

Moreover, the dose range is somewhat truncated in terms of the overall doses that were administered to the animals, so that our inferences in terms of the underlying logic of a dose response may be somewhat limited in this case.

Overall, I would also agree that the findings here may transcend, or not easily fit into, the diagnostic criteria that this Program has usually applied. And I am in agreement with Doctor Ashby that the language on page ninety-three (93), perhaps more appropriately fits the conclusions that we might wish to consider as a Panel rather than the four criteria that are usually laid out for us.

I also hope that we will be able to make some recommendations as to the appropriateness of further study in certain mechanistic, as well as, overall bioassay type designs in connection with these findings.

Thank you.

DR. GALLO: Thank you, Ellen.

I'd like to move right up to the table.

Doctor Davis, go ahead, please.

DR. DAVIS: My comments, I think will be brief because I echo the sentiments of those who have spoken before me, but a couple of points, I think they're pointing out again, just to indicate the -- their importance to me.

The fact that females accumulated fluoride, yet did not show cancers, yet did show a toxic effect and yet we have no reason to suspect that they should respond differently. I see no reason why there would be a sexual effect, so I'm convinced that perhaps the tumor should not be considered as strongly as some would like.

The fact that one of the tumors was found in a site -- in a microscopic fashion it was found in a site not normally looked at, might also imply that we need to be very careful with using the historical control data, as well.

And that goes along with what the staff has already talked about, being the diet differences, and the fact that they use X-ray. So, I am somewhat concerned that we might over interpret the data based on what we've seen in controls in the past.

One question that I do have; given the size of the subcutaneous tumor, would it not have been possible to determine the amount of fluoride at that site in spite of the fact that you report that fluoride does not normally accumulate subcutaneously. It might have been interesting to know what the fluoride concentration was in that tumor.

And finally -- well, not finally, but with that same tumor, there was quite a bit of cartilage differentiation in that site, so I would imagine that perhaps some people felt somewhat queasy about calling it a osteo- tumor, in spite of the fact that they're perhaps more common subcutaneously than a cartilage based tumor.

And, of course, had that call gone the other way, we perhaps wouldn't even be concerned about the numbers, because that would tremendously change the statistics.

Finally, I think Doctor Garman's attitude toward looking somewhere else for a mechanism is very important. I don't know if his biological proposal is the right answer, but it does make sense that given that the females did in fact

respond, and that perhaps microfractures may, in fact, be occurring, also, the fact that the mice are housed individually, might -- they may not have as much trauma; there may be not be as much fighting; there may not be as many microfractures occurring to take his proposal one step further.

So, I think that kind of mechanism ought to be looked at, and I do agree with the findings of the report.

Thank you.

DR. GALLO: Thank you.

Jay?

DR. GOODMAN: There are two comments that I would like to make at this time relative to the abstract.

First, I think that the in the body of the abstract, it should clearly be noted that in this particular study there was extra scrutiny given to bone tissue in terms of microscopic analysis, and X-ray analysis that was not performed in the historical controls.

And second, with regard to the conclusion section in the abstract and the conclusion which appears in the body of the report.

There is a point here where it talks about based on the occurrence of a small number of osteosarcomas in dosed animals. I think that it's very important that the conclusion clearly reflect the body of the report, and what I would suggest is that after the term, "small number", that parenthetically it be noted that there was no statistical difference between the dosed and control animals.

DR. GALLO: That's it?

DR. GALLO: Okay. Doctor Hayden, any comments?

DR. DAVID HAYDEN: I basically concur with the results of the study, and I think the other speakers have eloquently delineated their efforts in terms of supporting this work.

It was very thorough, thorough as has been pointed out, more thorough than other studies that have been similarly conducted.

I would like to ask a few questions for clarification purposes.

On page thirty-seven (37) at the bottom of that page, there is a statement here which I would just like to mention to you to see if you could

explain it.

Says, "The fluoride content of plasma was significantly increased in the high dose groups, that's three hundred parts per million (300 ppm), and in the control group of male rats maintained on the standard NIH-07 diet."

This is curious that the plasma fluoride content levels in the high dose group were elevated, and in the control group of males were elevated.

And I thought we were using a low fluoride level diet here, so I would like to have for clarification on that, what the reason might be put forward for that finding.

DR. GALLO: John, would you like to respond?

DR. BUCHER: Yeah.

There were two control groups. There was a low fluroide control group or a control group receiving low fluoride in the diet and then there was a control group that was receiving the traditional NIH-07 diet, so we should probably clarify that that was not really a control group but it was a diet -- a different diet group.

So when compared -- when you compare the

plasma level in the low fluoride diet group to the plasma levels of fluoride in the group receiving the NIH-07 diet, as traditionally constituted there was a difference.

I'll clarify that.

DR. HAYDEN: Okay, I think it would be helpful to clarify that.

DR. GALLO: Yes, thank you.

DR. HAYDEN: I have another comment here just for clarification also, on page sixty-six (66), table fifteen (15).

I thought it was curious here that the -- in males, and we're talking about male mice here, and we're talking about the tibial cortex in increased osteoid, there seems to be an increase at the fifty parts per million (50 ppm), hundred parts per million (100 ppm), twenty -- two hundred parts per million (200 ppm), and then we get to three hundred (300), it drops off to zero, and at six hundred (600), again, it's a little bit lower.

This seems to be a little bit out of sync here and I just wondered if anybody had any comments with regard to that data.

DR. BUCHER: We don't have an answer for that

one, but we can go back and look and see if we can come up with something.

DR.. HAYDEN: Okay. I just thought it was curious if there was an increased incidence of osteoid as the dose is increased and then it dropped off to zero all of a sudden.

I think it's fairly evident in this study, it's -- it's quite doubtful that any osteogenic sarcomas were missed, however, it is also very interesting that one was picked up on microscopic evaluation of a bone that did not have any radiographic evidence of abnormality.

I guess that makes all of us think that there is always a possibility that we may miss things in any study unless everything is sectioned which is virtually impossible.

But I think in the context of this study everything conceivable was done to reveal the presence of bone lesions, and I feel very comfortable and very happy with the way the study was conducted.

Thank you.

DR. GALLO: Thank you, Doctor Hayden.

Doctor Gold, who had her hand up first in all

this.

DR. GOLD: I'd also like to commend the staff for an excellent report.

I have four points to make.

I want to underscore the fact that this is a highly unusual study for an NTP, bioassay because there is no zero control.

We are examining a narrow dose range which is -- which spans the normal dietary intake of fluoride by our control population.

Second, is that I want to underscore what Doctor Silbergeld said that this is a naturally occurring chemical, it's ubiquitous, we're all exposed to it, and the range for human exposure is rather narrow, potential human exposure.

And the difference between the animal study and the human exposures is not nearly as great as typical with synthetic chemicals.

Third, as to the thoroughness of searching for osteosarcomas, I just wanted to note that in a recent bioassay of nitrofurazone, we barely noticed the fact that the incidences were zero in control, for osteosarcomas; zero in control, one in fifty (1:50) and two in fifty (2:50). And this is three

in eighty (3:80) that we're examining so carefully.

To the extent that these are late appearing tumors I just want to note that the survival was excellent for male rats in this study.

And although the historical controls are probably not so relevant, because we've examined so carefully the results on osteosarcomas in male rats indicate that none of them was identified by radiograph, that they were all seen grossly except this one microscopic.

So, if we just look a little bit at those historical controls, we have an enormous group there, six thousand one hundred and thirty-one (6,131) animals that have been exposed to fluoride at a level between the low and mid dose in the study, and we only saw zero point six percent (0.6%) osteosarcoma.

DR. GALLO: Thank you, Lois. Barbara.

DR. McKNIGHT: I do want to commend the NTP for an extraordinarily thorough job in performing the study and writing up the report.

I do have a couple of questions about the design and analysis of the study, however.

I didn't find in here, and maybe I just missed

it, a statement about whether the cages were rotated in the study.

Were they?

DR. BUCHER: Yes, unh-hunh.

DR. McKNIGHT: And my other question has to do with the pair control group.

Was it maintained within the same room as the control on the dose groups?

Well, my big question about the analysis of the study is why the data from the animals in the paired control group were not contained in the statistical analysis.

Seems to me that that's ignoring some of the information contained within the study which may be important, particularly when we don't have the same comparability with historical controls.

DR. BUCHER: Well, the paired control group was originally added to the study to provide animals that would be killed whenever an animal in a -- in a dose group died.

These animals were then radiographed on the same radiograph as the early death animal, primarily so that we could have an age-matched control for looking at the density of bone, to try

to pick up fluorosis lesions.

The animals were not entirely -- this special control group of animals was not entirely examined at the end of the study.

In other words, those animals that lived to the end of the study and were not used at paired controls were not evaluated for carcinogenicity.

The animals that were killed during the study were evaluated for carcinogenicity, but there is a question about the appropriateness of using those animals because they were -- they were terminated in a manner that was not like any other animal in the study.

In other words, they were not moribund sacrificed. They were a healthy animal that was killed at the time of the death of another animal.

So, there are arguments for and against including the paired control group in -- as the main statistical analysis.

What we've chosen to do is use the base study animals to perform the primary statistical analysis. We have also performed the statistical analysis including the data from the paired control animals, and where there were differences that we

felt would influence the interpretation, we've brought that into the report.

And -- and you will find P values discussed in the discussion section, and I think several appear in the result section that concern what would happen statistically if one were to include the paired control groups.

So, I think this is the best solution, but there are clearly different ways of arguing this point.

DR. McKNIGHT: I understand that.

The statistical analysis that's generally use treats the tumors, the logistic regressions as it is used here, treats the tumors as if they were incidental findings of death.

That's really making the assumption that the prevalence of tumors among animals dying naturally is the same as the prevalence of tumors among animals that are living at that time.

So, in that sense the animals who were sacrificed at any point in time should be giving comparable information about the prevalence of tumors at that point in time.

I'm not aware of any statistical studies of

the statistics which show that in the absence of any toxic effects or toxic lethality of the chemical, or death due to other causes from a chemical, that tumors which are not quite incidental could cause problems with this test; and therefore I think it might be more appropriate to include at least the sacrificed animals if they were examined for -- for the tumors in the control group and -- in the statistical analysis.

DR. GALLO: Doctor Haseman.

DR. HASEMAN: I agree with what Doctor McKnight said regarding the -- I don't believe that treating a sacrificed animal as if it had died naturally for incidental tumors, it shouldn't matter.

But I'd also point out that this report has three hundred and fifty (350) pages of appendices. We had to decide and make a decision as to -- you know -- what level of detail to present.

As Doctor Bucher said, we did present, we did -- you know -- carry out both sets of analyses, and rather than present them both in the report we elected that it would be -- NTP decided it would be preferable to do the more limited analyses and

bring in the others where they were necessary.

Most of these paired sacrifice controls had no tumors at all. They were all sacrificed early in the study, so they didn't contribute a lot of information.

I think the two places where they did, we brought them in, one of the early saced animals had an oral cavity tumor, one of the controls, so that weakened the effect a little bit.

And I think one of the interim sac, high dosed animals ha a thyroid molecular cell tumor when we brought it in.

So it's not that we're ignoring the data. We did evaluate it carefully, but we were -- we -- the decision was made to just bring it in as -- as needed where it would help us interpret the study and we intended to do that.

DR. GALLO: Thank you, Doctor Haseman.

Doctor Eustis?

DR. EUSTIS: Yes.

I'd like to point out, that -- that really no tumor is truly incidental.

Certainly, if you have a -- a pituitary tumor that's secreting prolactin it might affect tumor

genesis of the mammary gland.

And, so they're are interactions between tumors, and there are also other conditions such as hypothy- -- thyroidism that might affect tumor development or kidney disease that might affect other kinds of things.

So, I think in this situation, where you have populations of animals that are different; in other words, animals that were sacrificed while healthy are not truly comparable to animals that were killed because of some other condition.

DR. GALLO: I think what we're getting into is a biological statistical discussion, and I don't want to truncate it in any way, but unless there is further debate on it, I'd like to move on if we can.

Is that okay? All set.

Lauren? Doctor Zeise?

DR. ZEISE: I'd like to echo the remarks of several of the other Panel members that said that the report was very well done.

However, some have indicated that there is the need for another study, and I agree with that.

I think there is a need. The bone

concentrations seen in the dosed animals are within the range of those seen in humans, and the range given in the report for drinking water concentrations of point one (.1) to point four (.4) ppm are very close to those that are seen in the treated animals in the study.

So, I think it's important to realize that even though the water concentrations were higher than what we see, or what humans are exposed to, the bone concentrations were not.

I think we have to be very careful about the choice of dose for the next study. Therefore, I think we should probably go beyond what was used in this study, and even though that might increase mortality, I think that will lead to more definitive finding.

I'm concerned about the oral cavity tumors in the male rat. There were also two rare squamous cell tumors of the nasal mucosa, and I think those should be brought forward in the report for the male rat.

I think a future study will resolve some of these issues, though.

Thank you.

DR. GALLO: Thank you.

Doctor Carlson?

Any response? Got any response to that? (looking to Doctor Eustis)

DR. EUSTIS: No, I'm certain that what you're talking -- in reference to the two nasal cavity, squamous cell tumors, I believe those are metastatic tumors from a --

DR. ZEISE: No, they were primary -- there was a primary papilloma and a primary carcinoma according to the table in the back of the report.

DR. BUCHER: Not sqaumous cell carcinomas?

DR. GALLO: No.

On the question bone level, I think one thing we have to keep in mind is there are many experts on -- on bone fluoride here in the room, but the bone tends to be an integrater here, so I think we have to at least take that into account, that there -- it's gone both ways.

And I'd like to move on to Dr. Carlson who has a couple of comments.

We're pretty much on schedule.

DR. CARLSON: I thought you were going to make Doctor Zeise, the last, as usual. It's a Z, but --

DR. GALLO: No, no.

DR. CARLSON: I'd like to compliment John, like everybody else, on the writing of the document, and on the clear logic, and I realize it took a lot of extra time to do that.

And as we went through a lot of the re-wording of every document yesterday, I think it's pretty clear that we're very happy with the logic and the explanations that were given.

And I think this is also true in your presentation on the sequential thinking about how you got from -- you know -- looking at the numbers to trying to decide what the mechanism might be to how realistic it was in putting in the statistics.

And I think I buy that for these bone tumors, but I have trouble when I look at the papillomas in the oral mucosa, and I think that's what Lauren had alluded to, that in fact, that if you -- couldn't you use the same sort of rationale there for the -- you know -- increasing numbers, and yet nothing is quite different, and you could certainly think about a mechanism for the irritating nature of the fluoride.

I just -- perhaps you could walk me through

that, sometime.

DR. GALLO: That's your only comment? Can't believe it.

DR. CARLSON: Well, that's a big one, because I could go either way with that because if you could -- if you could convince me that the oral mucosa lesions are -- are negative, then I'm not sure about the bone ones. We should not make them less than equivocal.

DR. GALLO: I'll leave it at that.

DR. BUCHER: Let's then consider the oral cavity mucosal tumors, on page fifty-six (56) of the report there is a table.

(Panel members refer to report.)

I think one of the things that's been lost in comparing the bone tumor data to the -- to the oral cavity data is the fact that we ddi get a statistically significant increase in trend in the bone tumors, but the oral mucosa tumord we do not have statistical significance with any of the tests for either males or females, and when one -- when one even goes to the extent of combining -- ignoring sex and combining the male and female data, we still do not achieve statistical

significance for the incidence of these tumors.

In bone we don't have a recognized preneoplastic lesion for the osteosarcomas. In -- in the oral cavity, we do have a recognized preneoplastic lesion, and that's the squamous hyperplasia here listed on the tongue because that's where the ones that appeared were coded.

Those do not increase, and we think that this is important in the evaluation of these tumors.

I think that the strength of evidence is less for the oral cavity. We have a carcinoma that has appeared in the females in the control group. We also had an oral cavity tumor that appeared, I believe, in the special control group animals in the males.

So, in comparison with the bone tumors, we had no tumors at all in either the low dose or the control animals in the male rats, or in the female rats there were no bone tumors seen at all in any of the groups.

So, I think we're dealing with a different level of confidence. We're not very confident in the bone, and we're even less confident that the oral cavity tumors are chemically related.

DR. CARLSON: I have a little problem with the preneoplastic argument, because we keep getting that response, and then Scott comes up and says the tumors just don't appear. So, sometimes we get tu-- -- just have a little problem with that.

Scott, do you accept that more for this particular type of tumor?

DR. EUSTIS: Well, I certainly think that if you -- if it was looked at closely you should see some preneoplastic lesions. Now, you might consider the -- the papillomas as being --

DR. GALLO: Unh-hunh (yes).

DR. EUSTIS: -- a part of that of that preneoplastic process.

But, again, I'd just like to echo it, what John said, is -- is that there is a different level of confidence here in that we did find a squamous cell carcinoma in the control females.

And as John mentioned, there was also squamous cell carcinoma in this special control group of -- of the males, that -- that we have not put into this table.

So, we have a level of confidence that's not great to begin with and there are these

other factors, statistics and then the tumors in the controls that -- that give us even less confidence.

DR. SILBERGELD: But one of those controls is not controls. You keep referring -- excuse me, but you keep referring to them both as controls, and as Doctor Gold pointed out one is not really a control, or in any event they all are arranged on a hierarchy of different doses, and to consider them both as controls is misleading.

DR. EUSTIS: You can make that argument for any tumor in this study.

DR. SILBERGELD: That's right.

DR. EUSTIS: For instance, you have to consider what we have, and these are the controls, for this study.

DR. GALLO: Doctor --

DR. HART: Use the microphone, please.

DR. GALLO: Yes. Doctor Davis?

DR. DAVIS: I guess in the midst of my comments were two questions that I didn't get a response to.

The first was -- was fluoride level measured in the subcutaneous tumor, and can that be done if

it wasn't.

And second, was there much discussion about the call of the subcutaneous tumors since there was quite a bit of cartilage?

DR. BUCHER: We did not measure the fluoride level in subcutaneous tumor, and I -- I'm not sure if we could. I know we have a certain amount of that tumor left in the fixed material, so we can see what we can do.

Scott may want to mention --

DR.. DAVIS: I think the reason for that is because we're making a bid to-do that bone accumulates fluoride, and --

DR.. BUCHER: (Interposing) Well, it's a matter of cause and effect. I mean, if you -- if you want to say that the subcutaneous tumor is induced by the fluroide that has accumulated in a tissue that is not ossified until after the sarcoma develops, then you can't put the cart before the horse to attribute it to -- to the accumulation of fluoride in the tissue, since it's not the same as the bone --

DR. DAVIS: (Interposing) You're saying it's possible that the accumulation occurred after the

tumor has been created?

DR. BUCHER: (Interposing) That's right. That's right.

DR. DAVIS: I'll buy that.

DR. GALLO: I think that there is another thing that should be considered in -- in the subcutaneous tumors, and the pathogenesis of those -- of those osteosarcomas, they can be induced -- it's in the literature that they can be induced by simple injections.

DR. DAVIS: Right.

DR. GALLO: And there is a lot of bone tissue or osteoid type of tissue in those -- at those injection sites, and I guess you could speculate that they became a fluroide sync, but I don't -- I don't think we have evidence one way or the other at this point

Doctor Gold?

DR. GOLD: As we discussed this report and I look at the zero ppm all the time in all the tables, I -- I guess I have some concern about that.

I -- I want to thank Doctor Bucher for making the slide that he made which I had asked for on the

milligrams per kilogram per day dose to animals in the four groups, plus the historical controls.

Most fluoride that rodents receive is from the diet, not the drinking water.

And I guess I'd like some -- In a way, I'd like to see milligram per kilogram per day estimates in the tables so that zero ppm doesn't give the impression that we have a zero control group.

DR. GALLO: That's another internal comment that I think we can deal with.

DR. GOLD: And I think that table could go into the -- I think that table could very nicely go into the text, as well.

DR. GALLO: John, do you have a response?

DR. BUCHER: I agree that the table will go into the -- the text of the report.

We will make several other additional tables concerning bone fluoride -- graphs concerning bone fluoride accumulation and such things.

We could -- I agree the zero ppm is not appropriate. We could simply call it the control, and then define the control as being a certain amount of fluoride in the diet at a particukar

time, or we could, I suppose, look at the -- putting in actual --

DR. GOLD: (Interposing) I think it would be clearer in reading the report if it was in milligrams per --

DR. BUCHER: I agree.

DR. GOLD: -- kilogram per day.

DR. BUCHER: Now. but -- well, the -- I hate to assign the actual level based on the rough estimates from dietary absorption that we have because I'm really not confident enough that we want to put those kind of numbers out for someone to run risk assessments on, because I just don't feel those numbers are perhaps as good as others.

DR. GALLO: I think an alternative for that would be to -- on the major tables, to state what the dietary levels were of the zero -- of the quote "zero controls".

That way you have it, and -- and you can still say that your experimental groups, if you will; that is, the groups in which the fluoride were added were zero twenty-five (.025) and -- and have that -- you can even footnote it.

I mean, the point you want footnoted is that

at zero it is not zero.

And that's the point you need.

DR. GOLD: Yes, I think it would be better to call it "control" in the table than "zero".

DR. BUCHER: That's --

DR. GOLD: (Interposing) I can go along with having a --

DR. BUCHER: (Interposing) That's why --

DR. GOLD: -- a statement with the milligrams per kilogram per day.

DR. GALLO: Dr. Carlson?

DR. CARLSON: Yes.

DR. GALLO: And then Doctor Ashby.

DR. CARLSON: Before we change the subject, only the fact that the milligram per kilogram per day changes with time --

DR. GALLO: Absolutely.

DR. CARLSON: -- and that can be very confusing if you put that in there, so how do you --

DR. GALLO: (Interposing) That's the importance of the bone level, which is the question I will ask --

DR. CARLSON: -- so Lois' idea is an excellent

one.

DR. GALLO: -- when I get around to getting a question in.

Doctor Ashby and then Doctor --

DR. ASHBY: Let me just track back to the discussion between Doctor Silbergeld and Doctor Eustis just now when you said that two controls are not controls, and you said that you can say that about the whole study.

Were you talking about this same problem that there is fluoride in the controls?

Is that what you meant?

DR. GALLO: Yes. I hope that's what he meant.

(doctor Eustis nods affirmatively.)

DR. GALLO: I thought that was -- I think your point earlier, John, that we have data on over six thousand animals for this fluoride is an important one; also that should not be lost in the shuffle.

Dr. Carlson?

Oh, no, I'm sorry.

When you get down to that end of the table I get confused with the distance.

DR. ZEISE: Just another another caveat on this issue; the tables in the back of the document

give bone concentrations for different exposure periods, and perhaps if you referred to these in that context, that will help.

DR. GALLO: Yes.

If I get my comment in that was going to be one of them, so you have just taken one away from me.

Are there any other comments from the Panel?

Mine, yes.

Two things. One, I'm not going to comment any further on the report, itself. I thought as Doctor Ashby said, there is a few of us that have sat around this table tht have some historical perspective for this thing, and this is an excellent report.

And I want to in compliment the NTP, and you particularly, John and Scott, for doing a good job on it. It's thorough. It goes into the historical background, and I -- it's an example -- one of the examples of designing a study around a composed -- truly around a working hypothesis, and not just, we're going to test the chemical, and I think that that's an important factor that has to be brought out.

There are a couple of things in the report I would like to see. I would like to see a graphic presentation of the bone levels by dose, by species, and by gender.

Whoops (spilled water.)

And I think that would help us and I think that gets back to it; more of the same.

The other thing on the mechanisms, I find it intriguing from an experimentalist and a clinical point of view that osteoporosis is -- is very prevalent in the female -- human female, that it's controlled and in some respects are aided, ameliorated by estradiol and other types of additives.

And here we have a compound and there are only two or three in the literature that I know of that do this that will take a uterine tumor, whether it be benign or malignant from, in this case, the concurrent controls at fifteen percent (15%), then a two percent (2%) and with a historical background ranging from eight to thirty-six percent (8-36%) down to two.

I will say this and I -- I guess I should -- while, there is another very interesting compound

in the environment that does something very similar and that's dy- -- that's TCCD; dioxin does the same type of thing, and we have no idea why, whether it's receptor mediated in controlling of the hormone receptors may be one possibility.

The one difference that I will say about this compound, about this element and all the others that I've seen, is that when you have a chemical that alters the receptor, it usually will alter breast tumors, as well as uterine tumors, and here we have a chemical that is selectively affecting, however you want to stay that, the rate of tumors in uterus alone, it's not affecting breast.

So, we have, again, getting back to the question of mechanisms, I think it's an important one. A couple of members of the Panel have talked about future studies.

I think the major thing that I would like to see on future studies is an effort to look for the mechanistic effects here. I think a bioassay may be important, and we're going to hear in some of the comments of other bioassays.

But I think we have to get that down to the mechanism of action of what fluoride is doing at --

at all these different sites.

And with that, if there are no further comments, I'd like to hammer a fifteen (15) minute break.

Let's get back here about ten -- I want to start sharply at ten thirty (10:30).

Thank you.

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(BREAK, 10:13 - 10:30 A. M.)

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DR. GALLO: Okay. What I'd like to do now is move into the segment of the meeting on public comment.

We have in your handout, I believe, nine or ten listed speakers and you'll see the order. If we have time at the end, I'll allow a few brief -- a few moments for other speakers.

I have one person that has also sent in a written comment that didn't make the list here, and what I'm going to do as I mentioned before, I'm going to hold everyone to seven minutes. We'd like to take this thing through to lunch, at about twelve thirty 12:30), if we do that we'll make it.

The general format is the presenters will come

to the podium up in front, make their presentation, there will be questions from the panel, if -- if they so desire, and then on to the next speaker.

It's going to be seven minutes. I'm going to set the timer and I would -- I would ask you to please respect that time.

And our first speaker is Doctor John Yiamouyiannis, Safewater Foundation, Delaware, Ohio.

Doctor Yiamouyiannis?

(Doctor Yiamouyiannis comes to podium.)

I'll -- I'll warn you at six minutes, okay. I'll just give you the high sign.

DR. YIAMOUYIANNIS: In 1977, Congress instructed the U. S. Public Health Service to conduct animal studies to determine whether or not fluoride causes cancer.

As a result, the National Toxicology Program retained the Battelle Memorial Institute in Columbus, Ohio to perform two studies, one on mice, and another on rats.

Doctor John T. Toft, II, manager of the Pathology Section at Battelle, was placed in charge of the NTP mouse study.

On October 28, 1988, after a year of analyzing these results, Doctor Toft completed the pathology narrative and final report.

The most significant finding was the occurrence of an extremely rare form of liver cancer, hepatocholangiocarcinomas in fluoride-treated male and female rats -- mice, excuse me.

Among male mice, no such cancers were observed among seventy-nine (79) in the control group. At eleven parts per million (11 ppm), the lowest dose used, one was observed among fifty (50) male mice; and forty-five parts per million (45 ppm), one was observed among fifty-one (51) male mice and at seventy-nine parts per million (79 ppm) three were observed among eighty (80) male mice.

Using historical controls and doing a binomial analysis of this, the odds of these results occurring by chance are less than one in two million.

Normally, we consider it significant one in twenty (1:20); this is one in two million (1:2,000,000).

Making these findings even more convincing are

the results with female mice.

In the control group, no hepatocholangiocarcinomas were observed among eighty (80).

At eleven parts per million (11 ppm), one was observed among fifty-two (52). At forty-five (45), none were observed among fifty (50). And at seventy-nine parts per million (79 ppm), three were observed among eighty (80) female mice -- female mice.

Based on these findings, and these findings alone, there was clear evidence of the carcinogenic activity of the fluoride in mice receiving eleven (11), forty-five (45), or seventy-nine parts per million (79 ppm) in drinking water for two years or less.

On April 11th Battelle released the results of the NTP rat study which showed a dose dependent relationship between oral squamous cell metaplasias and fluoride in both male and female rats.

Among male rats no squamous cell metaplasias were observed among eighty (80) in the control. At eleven parts per million (11 ppm), one was observed among fifty (50) male rats. At forty-five parts

per million (45 ppm), six were observed among fifty (50) male rats. And at seventy-nine parts per million (79 ppm), eighteen (18) were observed among eighty (80) male rats.

Similar results regarding oral squamous cell dysplasias were reported in a Proctor and Gamble study.

Combining the results of the NTP and P&G studies shows an exposure-dependent relationship between these precancerous changes and cumulative exposure to fluoride as measured by the bone fluoride concentrations.

In addition, the NTP rat study showed a dose-dependent relationship between fluoride and the number of male rats with tumors or cancerous oral squamous cells.

In the control group, no squa- -- squamous cell carcinomas or papillomas were observed among eighty (80) male rats. At eleven parts per million (11 ppm), one was observed among fifty (50). At forty-five parts per million (45 ppm) two were observed among fifty (50). At seventy-nine parts per million (79 ppm) three were observed among eighty (80).

The NTP study also showed a dose-dependent relationship between oral squamous cell metaplasias and tumors and cancers in female rats.

While no squamous cell metaplasias were observed among seventy-nine (79) female rats in the control group or amoung the fifty (50) female rats in the eleven parts per million (11 ppm) group, at forty-five parts per million (45 ppm) one squamous cell metaplasia was observed among fifty (50) female rats, and at seventy-nine (79), four were observed among eighty (80) female rats.

In the -- I'm sorry.

In the control group, one squamous cell carcinoma papilloma was observed among eighty (80) female rats. At eleven parts per million, one was observed among fifty (50) females rats. At forty-five parts per million (45 ppm), two were observed among fifty (50) female rats. And at seventy-nine parts per million (79 ppm) three were observed among eighty-one (81) female rats.

In male rats the NTP found that osteosarcomas, a rare form of cancer, were confined to rats in two high fluoride groups. None were observed among the eighty (80) controls, or the fifty (50) male

rats in the eleven parts per million (11 ppm) group. However, at forty-five parts per million (45 ppm), one osteosarcoma was observed among fifty (50) male rats. And at seventy-nine parts per million (79 ppm), four were observed among eighty (80).

Based on these findings, there is clear evidence of car- -- of the carcinogenic activity of fluoride in rats receiving eleven (11), forty-five (45), seventy-nine parts per million (79 ppm) in the drinking water for two years or less.

Other animal studies regarding tumors, cancers, and fluoride, like to point out that this is not the only one that is founded. In 1963, Doctor Herskowitz and Norton from Saint Louis University showed that increasing levels of fluoride increased the incidence of melanotic tumors in fruit flies.

In 1985 Doctors Taylor and Taylor from the University of Texas, found that one part per million (1 ppm) fluoride in the drinking water increased tumor growth rate by twenty-five percent (25%).

In 1984 Doctors Tsutsui and co-workers from

the Nippon Dental University found that exposure to fluoride transformed normal cells into cancer cells.

In 1988, this was confirmed by research done at the Argonne National Laboratories, who also found that fluoride promotes and enhances the carcinogenicity of other chemicals.

In human cancer studies, epidemiological studies by Doctor Dean Burk and myself were the subject of Congressional hearings in 1977.

During these hearings, the U.S. Public Health Service officials claimed that our results were not due to fluoridation but due to changes in the age, race, and sex composition of the populations examined.

We were able to show that these officials had made mathematical errors and had left off eighty (80) to ninety percent (90%) of the data. And that when these errors and omissions were corrected, their very own method of simultaneously adjusting for age race and sex, confirmed that ten thousand (10,000) excess cancer deaths per year were linked to fluo- -- water fluoridation in the United States; a link the U.S. Public Health Service could

notdisprove.

DR. GALLO: One minute, sir.

DR. YIAMOUYIANNIS: So, the NTP studies began.

Since then, three out of four U.S. courts have ruled that the preponderance of evidence shows that fluoridation results in an increase in cancer death rates.

The most impressive case involved representatives of the National Cancer Institute, the Royal Statistical Society, the Royal College of Physicians, and the National Academy of Sciences.

After listening to nineteen (19) days of testimony from these and other witnesses, just as John P. Flaherty, Chairman of the Pennsylvania Academy of Sciences, and the presiding judge stated, quote, "Point by point, every criticism the defendants made of the Burk-Yiamouyiannis Study was met and explained by the plaintiffs. Often, the point was turned around against defendants. In short, this Court was compellingly convinced in favor of the evidence of plaintiffs."

I'd just like to make one final conclusion if I might.

Based on this, I recommend that this committee

determine that the NTP animal studies provide clear evidence that fluoride is carcinogenic.

Furthermore, on the ability of fluoride to cause genetic damage, to induce precancerous cell changes, to induce cancer, and to function as a cancer promoter, and based on the epidemiological findings strong enough to prove by itself in Court that fluoridation is linked to cancer in humans, I recommend that this committee find that fluoride is a class A carcinogen and that it be regulated as such.

DR. GALLO: Thank you.

That, by the way folks, is the format that I would like to follow. That was just seven minutes and a few seconds, and it was directed at the study with a concluding remark.

And thank you very much, sir.

Are there any comments or questions from the Panel?

Doctor Silbergeld?

DR. SILBERGELD: Thank you for raising the issue on the liver cancers.

I wonder -- Doctor Eustis, could you go over again, for those of us who are not experts in the

field of liver cancer, the decision to treat these cancers in the way that you have in the report?

DR. EUSTIS: Yes.

First of all, hepatocellular carcinoma can have a variety of phenotypes that are expressed in it, in its reflection of -- of the fact that these are malignant neoplasms.

In some of these animals, there may be some bile duct proliferation.

If the bile duct proliferation is extensive enough and it's believed to have become a primary part of that neoplasm, it may be called a hepatocholangiocarcinoma.

Similarly, some of these neoplasms may show a phenotype that resembles fetal hepatocytes, in which case the neoplasm is called hepatoblastoma. So, these names are given to hepatocellular carcinomas which show some differentiation in prolonged lines more torwards a fetal hepatocyte or towards a bile duct, but they are nevertheless in a hepatocellular carcinoma.

And we feel they are appropriate combined with the hepatocellular cardi- -- carcinomas in adenomas for evaluation.

DR. YIAMOUYIANNIS: Could I respond to that, please?

DR. GALLO: You can respond, surely.

DR. YIAMOUYIANNIS: Yes, I'd like to respond to that, first by saying that we have Doctor Melvin Rueber whom we've retained to answer that question at a later point.

DR. GALLO: I'm sorry, you're out of order, sir.

DR. YIAMOUYIANNIS: Why? I thought you said I could comment.

DR. GALLO: Okay. You can comment but we're not going to --

DR. YIAMOUYIANNIS: (Interposing) Well, that's what I'm doing.

DR. GALLO: Okay. All right.

DR. YIAMOUYIANNIS: I just wanted to preface my statement with that if that's all right.

DR. GALLO: All right.

DR. YIAMOUYIANNIS: But I will say that again, doing the research that I did, I talked to the pathologist at the Battelle Memorial Institute, Doctor John Toft who pointed out this is clearly, entirely different than anything he had ever seen

before.

So, we're dealing here with something that you can throw into a big bag, you can throw it into the bag of cancers, if you want to.

The NTP did exactly the same thing with the squamous cell metaplasias. They threw it into a more general heading, in my view, obfuscating what this Panel should have seen.

DR. GALLO: I think it should be pointed out that when any study, not just this study but when any study, comes out of the test laboratory, the pathology has not been reviewed by the PWG until the point that we basically see it here.

And I think those are the data -- you're taking of raw data at that point.

DR. YIAMOUYIANNIS: Actually, I'm talking about the final report from Battelle and also a --

DR. GALLO: Yes.

DR. YIAMOUYIANNIS: -- mention by Toft that he was not considered for the final review committee, --

DR. GALLO: (Interposing) That is --

DR. YIAMOUYIANNIS: -- whereas, the reviewing pathologists were considered for the reviewing

committee, so there is only one way the review committee could have come out anyhow.

DR. GALLO: I would -- I would disagree with that.

DR. YIAMOUYIANNIS: Okay.

DR. GALLO: Thank you very much.

Are there any other comments?

All right, Doctor Ashby, unh-hunh (yes).

DR. ASHBY: Just for point of clarification, I think that the phrase, "transforming normal cells into cancer cells is rather remotive, and not the best way of describing cell transformation."

If that statement were interpreted as implied, then we would no longer be here. We'd no longer be needing to do rodent cancer bioassays.

There still is a need to do rodent cancer bioassays. And an example, just to put the other side of the coin, caprolactan a compound which has been through the NTP bioassay program and came out as noncarcinogen to rats and mice.

And the International Association of Research in Cancer in Leon classified it as, I still -- I think it's still the only human noncarcinogen in that compound to transform normal cells into

cancer cells in the same cell transformation, assays so we need to have caution in the interpretation and should have only remotive praise that should help the cause.

DR. GALLO: Doctor Zeise?

DR. ZEISE: I have a question about the reclassification of the oral squamous cell metaplasias.

Were these in the oral cavity, and if so what did -- what were they reclassified to?

DR. YIAMOUYIANNIS: These were not in the oral cavity -- these were changes involving the ameloblastic layer of the tooth.

DR. ZEISE: Okay.

DR. YIAMOUYIANNIS: And in fact, this layer of ameloblast as the -- as they grow and after they go through the transition phase and maturation, they actually become the squamous cells which are outside and line the -- the gingiva.

So, we -- the PWG felt that the squamous metaplasia was totally inappropriate. It is a degenerative process and not a preneoplasty -- not a preneoplastic at all.

DR. ZEISE: Thank you.

DR. GALLO: Doctor Carlson?

DR. CARLSON: I -- I would just like to clarify something for the audience as far as the way these pathologist working groups operate.

I sat on a number of these myself, and there is no -- there is no pressure on the part of the NTP to lead a pathologist to a particular diagnosis. In fact, the diagnosis is not even suggested. They're given the slides to look at, in blind fashion, you don't know what the original diagnosis was, and the final diagnosis is a consensus of all the pathologist sitting around the table.

So, there is no way that the NTP would try to instruct a pathologist that they would prefer one particular diagnosis over another.

DR. GALLO: Thank you.

DR. GALLO: Final comment?

DR. YIAMOUYIANNIS: Yeah, I'd like to make a comment on that.

The comment is -- is simply that you would expect that if you're going to have the quality assurance pathologist be -- I don't even know why the quality assurance pathologists was -- was again

on a -- on a separate review committee. I would think you'd have a totally independent --

DR. GALLO: That happens to be the system. We --

DR. YIAMOUYIANNIS: (Interposing) But, if you do, then you should at least have the original pathologist on there as well as so they could discuss the results in a -- in an equal basis. I mean, you have two people disagreeing, and then you're putting just one of the parties on the group.

If we conducted our hearings the same way --

DR. GALLO: (Interposing) No, no. I think you're out of order on that. You don't understand the system. I think it would be wise to --

DR. YIAMOUYIANNIS: (Interposing) Well, I'm just saying that the system may be that way, but it leads to the bias that brought this screen report in front of the members of this Board.

DR. GALLO: I -- I've been associated -- I'm not a member of NIEHS, and I've been associated with these working committees for a long time, and I think that all of us can agree that have done anything with this that the review process of the

pathology, particularly, is -- is blinded as Doctor Garman has said, and they have pathologists in many walks of the field, experts in the area.

And I really don't believe, and I don't know how it other people feel, I'm speaking as an individual member here, I don't believe that there is any undue pressure. It's done as Doctor Garman has said. It's read blindly and there's consensus.

DR. YIAMOUYIANNIS: Okay, if I can address the blind issue.

Even if you're reading slides blind, and you declassify has having -- was done in both control and the -- and the experimental groups, if you declassify cancers and precancerous growths, as to eosinophilicphote and things that are not cancerous, it doesn't make any difference whether you know which is which, the blind just dies when you declassify cancer cells to noncancer cells.

DR. GALLO: That's -- that's not true when you're loooking at controls.

I mean, yes, the lesion is there, but you have no idea whether you're talking about dosed or undosed.

DR. YIAMOUYIANNIS: (Interposing) Right. But

if you reduce everything to zero, --

DR. GALLO: I'm going to -- I'm going to the piority of the chair and cut it off, because we've had almost a full fifteen (15) minutes.

Thank you very much.

Doctor Allaben?

DR. ALLABEN: Mr. Chairman, I suggest maybe a clarification of the role and responsibilities of the Panel is primarily and only to assess the study that's being considered and not take into consideration --

DR. GALLO: (Interposing) That has been -- that has been stated, yesterday, and it's been stated in every meeting, and I think the audience should know that what the Panel is doing is reviewing the study as reported, and we are -- we accept outside comment, but it is not part of the study design.

Thank you.

All right. The next speaker is Dr. James Bawden, University of North Carolina Dental School.

Doctor Bawden?

(Doctor Bawden comes to podium.)

DR. BAWDEN: My name is James W. Bawden, I'm

an alumni and Distinguished Professor, Pediatric Dentistry at the University of North Carolina, School of Dentistry.

I appear today as an interested scientist who's conducted research on the metabolism and clinical use of fluoride for twenty-five (25) years and who has published ninety (90) articles on the subject and on mineralized tissues in general in refereed scientific journals.

I also appear as a representative of the American Association for Dental Research and the American Association of Dental Schools.

These organizations represent over thirty-five hundred (3500) dental scientists and educators in the United States.

Speaking for these organizations and myself, I wish to say that we feel that the results of the NTP study give no indication that fluoridation of municipal water supplies is unsafe.

Some of our specific observation and comments are as follows: first, we wish to suggest that the description of the enamel organ dysplasia that appears in the first paragraph on page thirty-nine (39) of the Technical Report can be made more

accurate.

Because of the time constraints, I will not discuss these details, but we have submitted them in writing.

A second point concerns the plasma fluoride levels recorded for rats. It relates specifically to comments made by Doctors Silbergeld and Hayden at this morning's discussion.

The data reported for the six months drinking water studies are so inconsistent and illogical that we suggest that they be disregarded. We believe the problem occurred because the assay failed to include the acid diffusion technique even though the plasma of calcium fixed in ash.

The method is not the standard used in the current peer review literature.

The values reported were below the linear part of the standard curve observed by the fluoride electrode except for those reported for the hundred seventy-five ppm (175 ppm) sodium fluoride groups.

If that was not the problem, serious contamination of the samples occur.

Concerning the plasma fluoride in rats after twenty-seven (27) and sixty-six (66) weeks of

exposure, the values appear to be more reasonable and logical except for the control groups which were obviously overestimated by at least a factor of six.

The studies in the peer reviewed scientific literature consistently report plasma fluoride concentrations of point o one to point o two ppm (.01-.02 ppm) for rats drinking deionized water and given standard laboratory chow containing thirty to forty parts per million (30-40ppm).

Two-year controlled rats in the NTP study consumed a diet much lower in fluoride content and I should -- and should have had plasma levels no higher than point oo one ppm (.001).

The error is to be -- be expected on the basis of the fluoride assay method used. In the dose groups, plasma fluoride concentrations approached or reached values that may be directly read with the lo- -- with the electrode with reasonable accuracy.

Thus, the mean values reported for plasma fluoride concentrations in the dosed groups must have been much higher in relationship to the true values for the controls than described in the

report.

The correct interpretation of these data is of considerable importance. It is perhaps a better indication of cellular exposure than bone levels where the fluoride is for the most part sequestered and that latter structure of the hydroxyapatite.

It is also of importance to point out that a hundred ppm (100 ppm) at the hundred ppm (100 ppm) level of exposure, the mean plasma fluoride values were already a mag- -- an order of magnitude higher than observed in humans consuming fluoridated wat at one ppm (1 ppm).

There we have some concern over the terminology used in the report particularly in view of the relationship of the plasma fluoride values that the doses are referred to as low, mid and high.

Within internal context of the study, that may be appropriate, but in terms of the biological response in the plasma, the doses should be referred to more accurately as high, very high, and extremely high.

To imply that eleven parts per million (11

ppm) fluoride is a low dose is -- is misleading. This is substantiated by the fact that the plasma levels observed in the eleven ppm (11 ppm) group were substantially raised above those observed in the human population drinking one ppm (1 ppm) fluoride in the water.

In the so-called mid dose group of male and female rats, the plasma fluoride levels were an order of magnitude higher than those seen in human populations drinking fluoridated water.

We understand why the high doses were used in the NTP study. That is not the issue. The issue is public misinterpretation of the nomenclature.

We urge that every effort be made to deal constructively with this semantic difficulty.

Fourth, the appropriateness and relevance of the rat model in the case of a potential risk between the fluoride and osteosarcoma is questionable.

We realize that the NTP study was designed for a specific purpose and the relevance to the human situation is not a matter to be considered within the context of the study per se.

However, at subsequent stages of

consideration, relevance becomes of critical importance.

In humans, osteosarcoma is pre- -- predominantly associated with long bones and seldom with vertebrae.

Yet, in the NTP study seventy-five percent (75%) of the osteosaromas were located in vertebrae. And only one in a long bone.

Another observation is that in human osteosarcoma occurs primarily as a primary lesion almost exclusively in young people.

It's thought to be associated with active bon growth.

DR. GALLO: One moment, sir.

DR. BAWDEN: Yeah, okay.

This lesion occurrs at fluoride -- when fluoride levels are typically low, and at an early age.

In these studies, the lesion occurred late. Also, in humans the skeleton ceases to grow in the third decade, and in this study, the skeletons continue to grow virtually throughout the lifetime of the rat, greatly extending the period of risk.

In summary, we restate our position that the

results -- the results of the NTP study do not indicate that fluoridation of water supplies is ill advised.

This position is supported by the community of scientists who are actively engaged in research related to fluoride and are most knowledgeable about the subject, and we appreciate this opportunity to state our position.

DR. GALLO: Thank you.

Are there questions from the Panel, comments?

Doctor Silbergeld?

DR. SILBERGELD: Thank you very much.

Could I ask the witness to comment on the appropriateness in general of rodents as models for mineralized tissue research?

DR.. BAWDEN: They're widely used; there are important differences as there is in any animal model.

They're widely used because they're convenient and inexpensive. I think in any studies that are done extrapulation to the human situation is always a matter of serious concern.

We use rats for studying the development of -- development of enamel and dentine because of the

continuously growing rat size which is a convenient model.

But there are important differences, and we simply cannot exstrapulate from one species to another with great confidence.

DR. GALLO: Thank you.

Doctor Davis?

DR. DAVIS: I would like for the staff to respond, if they would, to the appropriateness of the tests used to determine plasma levels of fluoride.

DR. BUCHER: Doctor Bawden is simply certainl an expert in the field of measuring low levels of fluoride in various tissues, and he's hit upon an area that -- that I think I'm in substantial agreement with his comments.

The whole field of measuring fluoride in plasma and blood has progressed through a number of different preferred methodologies over the years, and as each new method comes on line, it seems like the average levels that are reported in humans go down.

The ashing method that was used in the -- in our studies was published in 1977, and we first

used it in the 1979 study. But I think that we need to go back and try to re-evaluate those data in light of what is known today and try to put some perspective on the serum levels that we are reporting, so I agree with that. That's a good point.

DR. GALLO: Thank you.

Jay Goodman?

DR. GOODMAN: I find myself in agreement with remarks that you made.

The question that really is before us, now is an evaluation of this particular report, and the question as to whether the evidence in this report for the test animals should be considered as no evidence of carcinogenicity, equivocal evidence of carcinogenicity, some evidence, et cetera.

Could you address that particular issue, please?

DR. BAWDEN: I prefer to defer to other speakers, particularly, Doctor Stamm.

My field of expertise is more in the technical aspects of the data and particularly with the plasma levels. And we want it to be constructive; we point out that we thought that was an important

area of misinterpretation, particularly with respect for the body burden.

When we talk about the dose levels being narrow but -- but if these high dose plasma levels are reasonably corrent, then the exposure was -- was very high in terms of a biological context, because when you raise plasma levels by an order of magnitude, that's a real joke. And certainly these appear to have been -- that appears to have been the result.

DR. GALLO: Doctor Bawden, I'd like to, if I may, I think your point on the -- the low, mid, an high is a good one.

Again, it's a format very similar to the question that -- that I addressed before on the -- with Doctor Yiamouyiannis on the approach that's taken for these studies.

If you're -- you're correct, I guess the low should be a low dose tested rather than low, but I think for editorial reasons, and historical reasons, pharmacologists and toxicologists have talked about low, mid, high or -- and I think that's a -- there are some clarifiers in there. In the introduction we speak of those levels, and --

and you're absolutely right, there is a good possibility of misinterpretation of that.

And I think that, for the individuals who are involved in the risk assessment and evaluation of fluoride, that's something they're going to have to take into account, but for this committee, that -- those are the confines in which we are working, and we'll have to address it in -- in that type of context.

DR. BAWDEN: I understand that.

DR. GALLO: And I really do appreciate your -- your comments on the plasma levels. For those of us who have worked around cholinesterase inhibitors for the last thirty (30) years, it's the same type of situation we've had in measuring cholinesterase.

As you get more and more refined, and then something goes from experimental laboratories, such as yours to a, if you will, a clinical toxicological laboratory for general use.

And there is a transition time, and I think you can appreciate that.

Thank you.

John? Doctor Ashby?

DR. ASHBY: Doctor, given this -- that this

report will be read by an unusually large number of people, I'm just wondering if we can't actually take this point on board and redo the tables with the phrase, "lowest dose tested".

I know it will be abnormal, but I think it will be useful in this case, the less confusion, the better, I think. The tables --

DR. GALLO: I think -- we can do something as long as -- Doctor Carlson?

DR. CARLSON: Yeah, I'll debate that, but I don't think we should do it now.

DR. GALLO: That's right.

Okay. Thank you.

I'd like to move on -- thank you very much, sir.

The next speaker is Doctor Bob d'Amato from Proctor and Gamble.

(Doctor d'Amato comes to podium.)

DR. d'AMATO: Thank you, Doctor Gallo.

Proctor and Gamble has extensively reviewed the known animal and human safety data on fluroide.

Our assessment of these data is that human lifetime exposure to fluoride via dentifrice usage,

as well as from the environment, is safe.

We have reached this conclusion by weighing all the evidence including human epidemiology data, animal toxicity and carcinogencity data, including the current NTP studies, the cause of our own Proctor and Gamble carcinogencity study, as well as the biochemical and physiological cellular effects of sodium fluoride.

Our assessment is that the recently available carcinogenicity data did not change our conclusion that fluoride is safe for human exposure.

We have conducted chronic carcinogenicity studies with sodium fluoride in both rats and mice at independent contract laboratories.

While the analyzed portions of our mouse study is complete, the pathology and the final report from this study will not be available for several months.

We know, however, that the mouse study was compromised by C-type retrovirus which contaminated all groups, including controls.

Therefore, these data cannot be used to draw any scientifically valid conclusions about the carcinogenic risk of sodium fluoride in humans.

We believe the C-type retrovirus was also responsible for the induction of benign osteomas which were observed in all groups including controls.

Every osteoma we examined, both controls and treated animals was -- was associated with a C-type retrovirus.

None of the osteomas, even those observed early in the study, progressed to osteosarcomas, that no treatment-related malignancies were observed.

Of note, more osteomas occurred in the high fluoride dosed group than in the other groups. The most likely explanation for the increased number of osteomas is biological interaction of virus in fluoride at the osteoblast as opposed to a fluoride effect on its own.

An interaction -- an interaction is the most likely explanation because the osteoblast is the target cell for both fluoride as well as the ret- -- retrovirus.

Even if such an interaction occurs, however, and was demon- -- results demonstrated, it would not be relevant to human risk, because in humans,

unlike the mouse, there is no evidence that bone tumors, either benign or malignant have a viral etiology.

In summary, we believe that the only valid assessment of sodium fluoride carcinogenic potential in the mouse comes from the present NTP study.

In fact, we suggested to NTP prior to the initiation of their study, that they increase the dose levels to be certain their studies would adequately address the carcinogenic potential of sodium fluoride in the mouse.

Our chronic carcinogenicity study in the rats has been completed. There was no evidence in this study that sodium fluoride alters the incidence of preneoplastic or neoplastic lesions at any site in the rats of either sex.

One osteosarcoma was observed, and because it occurred in the low dosed female rats, it was not considered treatment related due to its singular incidental nature.

P & G's assessment of this study and that of two independent pathologists is that fluoride does not cause cancer in Sprague-Dawley rats.

Because we use very high doses of sodium fluoride, we did see treatment-related toxicities of bone and teeth.

These changes were not cancerous, nor precancerous but were the typical known responses associated with exaggerated fluoride levels required to reach the maximum tolerated dose.

These changes were characterized as dose and time dependent increases in hyperostosis of bone and degeneraive changes of the ameloblastic layer in teeth.

These toxic effects have been extensively published as a typical and expected response to high levels of fluoride in animals and humans, and at current levels more than two thousand (2000) times greater than a normal toothbrushing exposure.

The fluoride bone deposition in the study was consistent with this toxicity and was above -- above levels already known to cause such effects.

In the rat study we used Sprague-Dawley rats and administered sodium fluoride daily in the diet at doses of zero, four, ten (10), and twenty-five milligrams (25 mg) per kilogram per day of body weight. There was seventy (70) animals per sex per

group which started the study.

For a perspective, these doses were two or three times higher on a milligram per kilogram basis than those used in NTP study.

Additionally, the bone fluoride deposition was approximately three times greater than that observed in the NTP study.

We have submitted to the NTP for their consideration a prepublication copy of the study which has been peer reviewed and accepted by the Journal of the National Cancer Institute.

We have also reviewed carcinogenicity and toxicity studies for fluoride in other animal species.

Over thirty (30) additional studies have been done and conducted in both rat and mouse, as well as in mink, guinea pigs, sheep, horse, and cattle.

None of these studies showed any indication of bone carcinogenesis, even at exposure levels which produced significant bone toxicity.

Doctor James Shupe, of the University of Utah, has examined cattle exposed over the majority of their life to extremely high levels of fluoride, naturally occurring in drinking water and in food.

While these extremely high levels of fluoride did produce skeletal abnormalities, there was no evidence of osteosarcoma or bone tumors.

It should be noted that bone growth and physiology in cattle more closely resembles that of humans than those of rats.

DR. GALLO: Doctor d'Amato, one minute.

DR. d'AMATO: As recently as 1987, the well-known international agents with the Research on Cancer have reviewed all the known epidemiology data in studies on fluoride.

They concluded that the studies were, and I quote, mutually consistent in not showing the positive association between exposure to fluoride and overall cancer rates or rates of different -- of different cancers.

In conclusion, the aggravation of human and animal carcinogenicity data supports that fluoride is not carcinogenic and that human exposure to fluoride from all sources, including diet, drinking water and oral care products does not pose a risk of cancer to humans.

This conclusion is supported by the weight of scientific evidence which has failed to show any

consistent deleterious effect of fluoride in human health other than the known toxicities of bone increase produced by extremely high levels of fluoride.

Thank you.

DR. GALLO: That you.

Questions from the Panel?

DR. SILBERGELD; Doctor d'Amato, was -- one issue that came up in our discussion of the NTP study were the extremely careful methods that were used to examine mineralized tissue.

Were similar methods used in all the studies that you've reviewed, and in the PNC sponsored studies; that is, radiographic and very, very careful microscopic analysis of many different sites?

DR. d'AMATO: I can answer that one in a couple of ways. First, dissecting out the bone, itself, on radiographs were done of all female animals.

Secondly, --

DR. SILBERGELD: (Interposing) Not the male?

DR. d'AMATO: Pardon?

DR. SILBERGELD: Not of male?

DR. d'AMATO: No. Doctor Ashby alluded to, we assumed because it was not metabolized, that we wouldn't expect and anticipate a difference between males and female. We chose arbitrarily to radiograph all the females, and as you know, we did not see in males or females any -- any bone abnormalities other than the expected ones of toxicity.

We did look at extensively of femurs, vertebrae, and three to four bones of the -- of the skull, as well as since we had significant toxicities in the study, bones which had the hyperostosis and osteosclerosis were very extensively dam- -- evaluated.

And so we had a very extensive evaluation of bone. Interestingly, as Doctor Bucher mentioned, the expected locations of where you would get bone tumors, especially osteosarcomas are exactly in those areas of twenty percent (20%) in the head, twenty percent (20%) in the vertebral column, and forty (40), fifty percent (50%) in a long bone like femur, so we had a very extensive evaluation of bone.

DR. GALLO: Any other comments, questions?

Lauren?

DR. ZEISE: Did you say something about the level of viral contamination across the different dose groups and whether or not there was any intercurrent mortality seen?

DR. d'AMATO: We did have -- we did have some mortality in the study, of course, because we were at, if not even slightly higher than an actual tolerated dose. The -- it was not our evaluation but a pathologist's evaluation that the mortality was in any way related to the benign osteomas.

In terms of evidence, we did -- as I said, we did see a very similar mortality in the control groups, and two low groups, that the mortality -- we had two groups like the NTP had in their study, and child-effect control of the low fluoride NIH-type diet control, which fluoride was added to.

So, we basically had four individual groups if you divide them by sex. Across those, the incidence was approximately two to six percent (2-6%).

This is significantly higher than what you would expect in -- in the normal historical population which is significantly less than one

percent (1%).

So, that was in a sense in terms of the control groups -- that was our clue that something was going on in the study. The two low does groups, the four, and the ten milligram per kilogram at a very similar response, the high dose group was approximately thirty percent (30%).

DR. GALLO: Jay?

DR. GOODMAN: We've had some discussion here regarding the appropriateness of grouping some liver tumors together as opposed to considering different types separately.

Could you tell us your views on that?

DR. d'AMATO: I really don't feel I have the extensive background on liver carcinogenesis to comment --

DR. GOODMAN: (Interposing) In your particular studies, --

DR. d'AMATO: (Interposing) In our particular studies --

DR. GOODMAN: -- if there were liver tumors would they have been grouped together?

DR. d'AMATO: They would have been grouped as hepatocellular carcinoma.

DR. GALLO: Thank you.

Any other comments?

I have a couple of quick questions.

Doctor d'Amato, you -- you quickly stated on your dosing, and I just want to clear it up for the audience, you said zero, four, ten, and twenty-five milligrams per kilogram body weight.

For those of us around the table, that problem isn't a problem, but that is not equivalent to parts per million in the diet or ppm in the water.

And I think you ought to know that, and you did give the conversion which are two or three times the NTP study, in equal amounts of -- as -- of body weight as a denominator.

The other question -- or actually the question I want to ask you is, in your mouse studies, what type of bone levels did you see there in comparison to the NTP studies?

DR. d'AMATO: There were approximately also three times greater with a high dose approaching sixteen thousand parts per million (16,000 ppm).

DR. GALLO: Okay. Just for the record, --

DR. d'AMATO: Almost three times higher.

DR. GALLO: About -- almost three times

higher.

Thank you.

Yes. Yes, a couple of comments.

DR. BUCHER: I'd just like to add something about the comparison of the mouse studies.

These -- your -- your doses are adjusted as the animals age, --

DR. d'AMATO: Correct.

DR. BUCHER; -- such that sodium fluoride is added to the feed in different amounts throughout the study to -- to maintain a constant dosage.

In our studies, the amount added to water is constant, and I'd just like to point out that the high-dosed animals in the mouse study, in our study ranged up to about -- averaged eighteen (18) to nineteen (19) milligrams per kilogram per day.

And, in fact, during the first three months of the study in female mice, I think our -- our high doses were, in fact, higher than your highest dose.

So, I think this suggests something fundamentally different about the way the two mouse strains handle the fluroide and incorporate it into the bone considering that the bone levels were so

much higher in your study.

DR. GALLO: I -- I think that's a valid point that we're talking about, a very dynamic system in the bones as we've already heard, and there are going to be subtle differences.

Are there -- I'm sorry.

DR. ZEISE: One more question.

DR. GALLO: Sure.

DR. ZEISE: I apologize if you've already said this.

Have you seen osteomas in previous studies from this virus and in this strain of mice, or do you know what the historical incidence is for that?

DR. d'AMATO: The historical incidence of osteomas on -- of -- unfortunately there is not a lot of data on viral induced osteomas, and we have spent a considerable number of years identifying the virus, characterizing the virus, and typing the virus, as well as injecting it back into the animal.

But virally induced osteomas are not very well studied and basically the only thing I can tell you is that the historical incidence of osteomas, is most people don't -- once you get them, most people

don't look for what the etiology is, is less than one percent (1%).

DR. ZEISE: Okay.

DR. GALLO: Oh, yeah. Go ahead.

DR. DAVIS: Did you measure plasma levels and, if so, how do they relate to what they found in this study and by what method did you measure it?

DR. d'AMATO: We have -- we have some plasma data, of course, as an experimentally -- as an experimentalist, I really don't put a lot of stock in our plasma data, mainly because as many of these studies are designed as standard in a sense, I should say a standard routine, but there are certain -- something -- certain amount of regimen that goes into these types of studies, in many cases the animals are sacrificed at a considerable time after the animals are dosed.

And to put a lot of data into -- and a lot of confidence into -- term of pharmaco-kinetics, into that type of data generation, I think is not -- is not worthy of it.

We are currently doing, in conjunction with a number of collaborators, a fairly extensive series of pharmaco-kinetic studies which compare the NTP

rat and mouse study and our own rat and mouse study on a pharmaco-kinetic and dynamics basis. I think that's the type of data that really is useful.

DR. GALLO: And we'll -- and we'll see those data someday, I hope?

DR. d'AMATO: Yes, that data hopefully will be -- will be published and will help to integrate, at least, on a uniform basis, all the studies.

DR. GALLO: We've -- we've heard earlier today about experiments that should be done, it was obvious that the -- the pharmaco-kinetics and dynamics of fluoride under these situations should be one, and I'm glad to hear that somebody is doing it.

Doctor Silbergeld, and then Doctor Ashby and then we'll move on.

DR. SILBERGELD: Again, on the subject of the hypothesized viral fluoride interactions, what was the nature -- statistical nature of that interaction across the groups?

Was it additive? How strong was it? Can you tell us a little bit more about that?

DR. d'AMATO: At -- at this point in time, there is not a -- certainly, if you -- if you go

from an incidence of two to six percent (2-6%) to thirty percent (30%) that is going to be, and we did not do, but I would speculate, if I could, that that's going to be statistically different.

In our view, it certainly jumps out at you as probably being biologically significant.

DR. SILBERGELD: What was the difference? What was the increase?

DR. GALLO: Two to six, is that --

DR. d'AMATO: (Interposing) Basically, two to six percent (2-6%) in the control animals, or basically four different -- that's four different data points, two control groups, males and females, and so it's two to six percent (2-6%) in that group, and approximately thirty percent (30%) in the high dosed animals.

DR. ZEISE: And what was the rate of viral infection?

DR. d'AMATO: Clarify in terms of what do you want it in?

DR. ZEISE: In terms of numbers of animals per dose? Do you have that information?

DR. d'AMATO: What we -- of course, we -- I consi- -- we looked at approximately, as many

animals as we can get our hands on in terms of tumors, about twenty (20) or so were looked at.

All I can say is that every animal with a tumor had virus. I mean, there was -- there wasn't an animal that didn't have -- there wasn't a animal that had a tumor that didn't have virus.

DR. ZEISE: And what about the animals that did, do you have information on that?

DR. d'AMATO: We did look at some -- in doing viral studies, of course, theoretically, the entire colony and the entire group then is potentially contaminated, so what we did do was look at non-tumor bearing bones.

Approximately thirteen (13) were looked at as non-tumor bearing bones. In that we did find viral particles in three of them, one in control and two in treatment.

And so even bones which were not ladened with tumor were contaminated, and theoretically if they go long enough, they may express -- this type of virus is constantly infected, it is an intropic virus that constantly infects the osteoblast.

DR. GALLO: Thank you.

I'd like to move on, if I may.

Thank you very much Dr. d'Amato.

Oh, I'm sorry, Doctor Ashby has a comment.

DR. ASHBY: I just want to confirm two things. First of all, this mouse study is going to be published, is it -- it's not an abortive study?

DR. d'AMATO: No, we did not abort the study. We --

DR. ASHBY: (Interposing) It's going to be published.

DR. d'AMATO: We -- we cur- -- currently we will do a peer review of that study as we did our rat study, do a peer review of the mouse study, and if reasonable scientific conclusions could be drawn from the study, that will be looked at by the peer review group.

DR. ASHBY: And, secondly, in the rat studies no effects seen in the oral mucosa?

DR. d'AMATO: No. We did have teeth changes as Doctor Bucher and Doctor Eustis has indicated, but in terms of the soft tissue or the mucosa, we did not have pre- -- preneoplastic or preneoplastic lesions.

DR. GALLO: Thank you.

I just want to remind the Panel that we're dealing with out study and all -- and this other information is extremely important but it is ancillary to our test this afternoon, and I'm sure it will be this afternoon by the time our test gets here.

The next speaker is Susan Pare from the Center for Health Action.

(Ms. Pare comes to podium.)

MS. PARE: First of all, let me comment, even though it's probably obvious, I don't have a doctor in front of my name.

I represent the Center for Health Action, which is a laymen group, and consumer group, a grass roots organization with people in twenty-five (25) states that represent us.

And while my written comments might seem at first glance to be antagonistic, I am in no addressing these comments to any individual here, in general, but -- and in general, trying to look at the NTP in the -- probably in a larger overview in terms of how it was originated, in terms of how the study originated and the Congressional request.

And then to go into some of the steps that occurred, seemed to be to me to be a misrepresentation of data or possibly it could be a judgment call on some people's parts.

It has been referred to in the Panel's discussion earlier this morning and just recently by the -- Doctor d'Amato, that confidence is one of the things that is concerned with when you end up looking at the slides, and it becomes to a certain extent a judgment call and it also becomes a point of confidence in the data that you're using.

Well, I think that confidence is also something that the public has to take into consideration in -- pertaining to the study.

And it was -- in terms of the background of the material of why Congress requested the NTP study thirteen (13) years ago that the excess cancer death rates that were reported to them by the -- Doctor Yiamouyiannis and Burk were significant enough to have the study take place.

And the study was described by Doctor Herman Krabill at the Congressional hearings, as this would be the final study to confirm the negativity of the fluoride ion in causing cancer.

This comment leads me to question the objectivity of the study, and again, I'm not saying that any individual here is being nonobjective, but it leads me as a layman, if this one is a comment regarding the NTP study, that this study would be the study to confirm that it's negative. It seems to me that is a conclusion you shouldn't begin with when you're doing an experiment.

You shouldn't have any conclusions as to what something will be or won't be, that's why you're doing the study.

Furthermore, during the Congressional hearing, Doctor Kraybill misrepresented data stating to the committee that thirteen (13) studies showed fluoride doesn't cause cancer. Upon further discussion of this particular comment, Doctor Arthur Upton in a subsequent meeting with Doctor Yiamouyiannis admitted those studies referred to had nothing to do with fluoride and cancer.

Doctor Upton from the National Cancer Institute agreed to have Doctor Yiamouyiannis serve on the protocol committee which was to design the NTP study on fluoride and cancer.

And as you all know, Doctor Yiamouyiannis was

not consulted.

And I understand from the length of time that this study has taken to be completed, that it was or- -- requested in 1977, and it is now, 1990.

Personally, when I found out that the NTP was doing this study some seven (7) years ago in 1983 when I first found out about it, I heard the results were going to be out in 1988.

I thought that was long enough and then we waited another two years. So, again from the public standpoint, thirteen (13) years from the time Congress requested the study to be done to th date now of its completion, and your review, seems like a long time to me from a consumer's standpoint -- if it takes that long for Congress to request a study, and the study to be done on a single carcinogen, it leads me to question the efficiency of the system.

In regards to the diet, I think -- there -- there have been many questions raised about the control diet and -- the two control diets, what it seems to be.

And in listening to the information this morning, in my own mind, I -- I would think that

from your historical controls and the diet that has been used and seemingly insufficient to actually make comparisons, because of the high fluoride diets that was in the earlier control, that in the future, the NTP will use a control diet that would therefore be something that would be comparable, and would have as low -- as low a fluoride content as possible.

If eight parts per million (ppm) is as low as you can go, then it would seem you would incorporate that kind of control diet in the future, so that then he would historical controls that you could actually use as comparisons, in future work.

In continuing, in terms of my criticism, I guess, of the -- what has taken place in terms of the NTP diet, or the study, I'm sorry, the reclassification of the liver cancer seems to have -- be a big problem in my mind.

And -- and again, I think it's something that has to be translated to the public's perception. That's why all these people are here today, is because of what the effect of what you're doing today is going to be -- mean in terms of the

public, and the public's health.

And this reclassification of the liver cancer from the time it left Battelle until this time -- to now when you're speaking about it, it just doesn't seem to be justifiable in terms of -- even though I'm not an expert on it, I can see clearly from point a to point d to point c to point did that it has been changed and reclassified.

And it seems to me you then get away from science and you certainly get into a matter of opinion and judgment and subjectivity rather than objectivity.

And all of you scientists and doctors here today are not here to share opinions with us, as much as you are to share the data.

DR. GALLO: One minute, please.

MS. PARE: Thank you.

So, I don't -- I don't really understand how there can be so much subjectivity in something that's supposed to be so scientific.

Also, in terms of the connection of water fluoridation that's been brought up by the previous speakers and is now going to be brought up by myself, I have to note that in a press release by

the National Institute of Environmental Health Scientists on February 6th, a number of scientific statements were made regarding NTP study.

And then in one paragraph, a large sweeping statement was made by Doctor David Hoel, if I am pronouncing his name correctly, about the effectiveness and safety of water fluoridation.

While the end result of what you do here today definitely is going to have an impact on water fluoridation.

I don't -- (bell rings), boy that was a quick minute.

DR. GALLO: They're fast clocks.

MS. PARE: Okay. Let's see if I can finish that sentence.

While there is going to be impact on water fluoridation, I don't see how your scientific work should have a political statement involved in the work, itself, and as well as in your NTP draft report, I didn't understand why there were political statements in a scientific piece.

Thank you.

DR. GALLO: Thank you.

Any comment from the peer reveiwers or from

Doctor Bucher or Doctor Eustis?

I would like to just address one of your comments, if I may. And that is, the selection process for the panels, and the dosing, and the designing the experiments.

Again, historically, you are selected for this committee by several different individuals. You are nominated for your expertise in different areas, and the study designs are built around the expertise.

If you are not selected for this committee you may or may not be asked to be involved, and becaus an individual within an agency has said, Doctor Gallo, you're going to do such and such, that may not occur, and I -- I think that's at least worth mentioning to you from a historical perspective.

MS. PARE: I'd love to have someone here give me an answer to the -- how -- how liver cancer can be changed in and reclassified and -- you know -- again, to me it seems like a major judgment call on the part of scientists that are supposed to be coming up with something that's objective, and again it's a matter of confidence from the public standpoint.

DR. GALLO: I think that's a valid point. Doctor Longnecker is going to respond to it.

DR. LONGNECKER: I am a pathologist that's involved in making the sorts of interpretations that you're questioning. And there is -- there are different classification schemes and there are very close calls.

I think that the important thing to realize is that when we interpret studies like this, we don't know what the treatment was.

In other words, all of the specimens are being treated the same way so that if a control animal is reclassified, a treatment animal should be reclassified in the same way, so that it's a consistent matrix.

And I think that objectivity is there, although some close calls do have to be made.

MS. PARE: Unh-hunh (yes).

Can I just ask one further question that in terms of what's been considered high dose here, is -- was the highest dose used in the study two hundred parts per million (200 ppm)?

DR. GALLO: One seventy-five.

DR. BUCHER: It was a hundred and seventy-five

parts per million (175 ppm) --

MS. PARE: (Interposing) Parts per million.

DR. BUCHER: -- of sodium fluoride.

MS. PARE: Of sodium fluoride.

DR. BUCHER: Which is about seventy-nine parts per million (79 ppm) of fluoride.

MS. PARE: You know -- again, I'm just wondering in terms of other contaminants that are regulated and that are considered cancer causing -- you know -- I mean, if you take a look at chloroform and benzene, or any of these other substances --

DR. GALLO: That has nothing to do with this one.

Thank you.

MS. PARE: Thank you.

DR. GALLO: Doctor Garman?

DR. GARMAN: I'd just like to add a brief point although I realize we're not -- we're really here to address the report, itself, but it has to do with the reclassification of liver tumors.

I think it should be realized that these large studies are read over a many month period, perhaps, six months, eight months, perhaps longer. And

you're looking at all of the lesions. When the lesion comes to the PWG, however, all of the liver tumors are looked at on one day, so they're all compared on one day, and I think the classification scheme that comes out of the PWG therefore is much more accurate, because it's not this temperal drift which may occur when the original pathologist reads an entire study.

DR. GALLO: Thank you.

It's always good to have pathologists and neurobiologists here.

DR. GOLD: I'd just like confirmation that that kind of thing happens frequently, it's not unique to this study.

I think maybe the public would benefit from knowing that.

DR. EUSTIS I'd like to make one comment. We have a lot -- twenty-five (25) or thirty (30) pathologists that have read studies for us over the years.

And with our use of historical control data, it's been very important to try to maintain consist terminology. And one of the primary functions of our quality assessment review is

try to maintain consistent terminology, so that we actually can use our historical data base.

If we had different pathologists use different classification schemes we would never be able to compare studies. We would not have a historical data base to compare to.

So, trying to use consistent terminology from study to study is a very important part of this process.

DR. GALLO: Our next speaker is Doctor John Lee from the Center for Health Action, Marin County, California.

Doctor Lee? It's a little early in the morning, eh?

(Doctor Lee comes to podium.)

DOCTOR LEE: It's eight thirty (8:30) in California.

I want to thank the committee very much for allowing me to speak.

My background is thirty-five (35) years in family practice. And there is a considerable difference between the practice of medicine and the level of scientific competence that is displayed here.

When you go to your doctor you may not realize that he may be choosing a life or death treatment for you on the basis of sixty/forty (60/40) rather than ninety-five percent (95%) confidence.

I have just a few comments I'd like to make about the study. Like all good studies, unexpected findings did occur, and I believe it's going to lead to further studies, and I have a short wish list that I would like to at least get my order in.

I wish that even more effort is placed on getting adequate controls.

The report of four hundred and sixty-eight (468) patients, or whatever it is, reveals that the controls were a wash with abnormalities, illnesses, tumors, atrophies, and this was very surprising to me, that rat controls can be supposedly the least of the affected animals, they can all be so ill, and there must be away to reduce the fluoride levels which would include starting with controlling the diet of the mother's of the rats or mice that are eventually chosen.

I was also very impressed that the nephropathy that is revealed in the report was not investigated very much. I would hope that in some of the blood

chemistries that a BUN and creatinine could be included, because it was evident that as the rats aged through the study their ability to excrete the fluoride decreased,

This was also reported in human studies, that with age, and that with exposure to fluoride the kidney loses its ability to excrete the fluoride.

I suspect this was going on, and I suspect that the BUN and creatinine was rising. It would have been nice to know what that was.

I was disappointed that over thirteen (13) years or eleven (11) years, whatever it was, of testing with rats and mice that no offspring of the exposed rats or mice were used in any way to discover any genetic effect.

Perhaps, other studies will take care of that, and I also was disappointed to see that in the earlier -- in the early remarks in the -- in the draft report, they did bother to mention that fluoride was used for preventing cavities and for treating osteoporosis, but they did not bother to mention that there are considerable contrary arguments to this, particularly the fact that in the last ten to fifteen (10-15) years, essentially

no study has shown that there is a fluoridation, per se, effect on the prevention of cavities, although there maybe a fluoride effect such as the topical application of the fluoridated toothpaste.

The amount in the water has become negligent -- negligible in its effect on the cavities, and also you should know that the osteoporosis references are out of date and are wrong.

Doctor Clearcopper and Doctor Riggs of the Mayo Clinic, since October have published results of the five-year study showing that treated patients in the osteoporosis fluoride groups had higher fracture rates, vertebral fractures were not prevented, and a number of vertebral fractures actually increased and they both agreed that fluoride should not be used for osteoporosis. It has the deleterious effect.

And that should probably be corrected.

Now, as I mentioned, the clinical medicine has to put up with incomplete understanding and especially incomplete knowledge of actual mechanisms of disease, or even how people get well.

This is something that we have to tolerate even though we should not be happy with it, we

should be trying to push the bounds of knowledge farther and farther out to find out what's really going on.

Recently, I attended the thirty-fifth (35th) annual reunion in my class, and it's amazing what happens to the confidence of doctors at thirty-five (35) years out of the medical school, and the fact of the rising skepticism and confidence in what we are doing.

A P value, however, zero point zero five (0.05) which is mentioned as the probability of the osteosarcomas, if you count the soft tissue sarcoma, and I believe you should, as four in the high fluoride groups, is point zero five seven (.057), very close to what in medicine is commonly accepted as a very good confidence level, ninety-five percent (95%) confidence level.

And it's a whole lot better than a lot of things that we have, so it's surprising to me that this is listed in a very arbitrary fashion. It seems to me as something of essentially no confidence just because it could occur by chance, one chance out of the eighteen (18) of something occurring by chance, and seventeen (17) out of

eighteen (18), it is occurring as a result of the fluoride.

In clinical medicine, this is excellent odds.

And I think that without intending to, the NTP study is going to be used by people as a way of judging the wisdom of adding fluoride to the public drinking water.

And I think that in that judgment there will be people who are going to be balancing risk versus benefit.

And it's been my experience that those people who study toxicology will often even accept the fact of the marvelous benefit, even though it may not be true but they haven't studied it; whereas, the people who do study the benefit part and find there really isn't very much from water fluoridation will then say, well -- without knowing, they will say, well, it really doesn't hurt anybody anyway.

I think that the NTP studies, if they say they're studying the toxicity, they should.

If have just one or two comments to make, I mean, they should stick to just the toxicity and not put any politics --

DR. GALLO: Actually, you have forty-five (45) seconds left. I'm not shortenening your clock.

DR. LEE: I wanted to mention that I didn't think the review of the genetic toxicity was as good as it should be.

The Ames test is clearly inapplicable here, Ames, himself, says so.

Proctor and Gamble study, he says now that he found a synergy between the vir- -- viral infection and fluoride.

That does not exclude fluoride as a possible cause of cancer. We don't know what causes cancer in people, and synergy is a legitimate possibility. I think that the work of Mohamed and Chandler should not have been neglected, and I think the fact that the Argonne study confirmed the (timer rings) _____ study should add some weight to the business of the transformation problem in the embryo cells.

Thank you.

DR. GALLO: Thank you.

Comments?

Doctor Bucher, you want to respond to this?

DR. BUCHER: There are just a couple of things

I'd like to comment on.

Concerning the nephropathy issue we have found, and it's been our experience that microscopic evaluation of the kidney is a better indicator of kidney damage than increases in BUN or creatinine, and there were no apparent treatment related increases in the property in this study, so I think we've addressed that point.

What I'd -- the other -- the other point I'd like to make is that the Riggs reference concerning the osteoporosis and sodium fluoride therapy is, in fact, included in the next line of that -- of the text that you've referred to.

DR. LEE: Right. That paragraph concerning osteoporosis starts out saying that it is being used to help us grossly, and then the last sentence says, yes, the Riggs testimony result is that it doesn't work.

I think the paragraph should be written so it isn't so conflicting.

DR. GALLO: I think -- I think what you want to say, perhaps what you're saying it's not -- is being -- and, in fact, it probably is still being used, but at least my reading, it may not be but it

certainly has been.

DR.. LEE: Right. Right.

DR. GALLO: I think that's an important point.

DR. LEE: And the kidney nephropathy occurred in the controls, all the way across, we're talking ninety (90), ninety-five percent (95%), as I recall, with kidney nephropathy.

DR. GALLO: Yes.

DR. LEE: I -- I don't -- I didn't realize that this was --

DR. GALLO: (Interposing) Geriatric rats are very much like geriatric people.

(Laughter.)

DR. LEE: I wish there was a way to distinguish, because it was apparent that the fluoride treatment was decreasing in the high treatment group rats, particularly.

DR. GALLO: Another point you made was on the question of the BUN and creatinine, and again -- and actually you answered it by talking about the chronology of this study which is thirteen (13) years old.

The modern studies that have evolved from this table bring in a lot of the mechanistic stuff and

work from working hypotheses rather than testing, and other things are being done and we appreciate those comments.

Thank you.

DR. LEE: Because in senile patients the BUN and creatinine rises, and it would be nice to know what the risk is.

DR. GALLO: And you had one other comment, and I'll use it as a -- I don't get this chance very often, thanks for setting me up.

Your question of the use of these studies, there are -- when you look at risk, in general, risk is generally considered to be a function of hazard and exposure.

What we're doing here as Doctor Silbergeld mentioned earlier is that we're looking at the hazard part of the equation. Other people, other experts in this room, and throughout the country, are looking at the exposure, and then when you get -- that gives you the risk.

So, you have the hazard and the exposure for the risk.

Then, we go to the risk management where the benefit question comes in. And I think that has to

be put in perspective, and I'm just taking the chance to give you two seconds on that, on risk analysis.

DR. LEE: Right. I see what you're driving at, but it seems to me it was inappropriate to put in a little bit on the benefit in a -- at the beginning of the -- of the draft report.

DR. GALLO: We, generally, in all the reports, the NTP and its reviewers generally want to see how the compound or the element order is being used in the public.

That's -- that's the reason that's in there.

DR. LEE: It's all right to say its being used but the way it says it, it -- it indicated that the fluoridation, itself, in the water reduces tooth decay, and that is not the evidence I --

DR. GALLO: (Interposing) I -- I think -- I think you could say they're -- they're -- you know -- and it would easy to adjust that.

DR. LEE: What I'm requesting is that contrary evidence also be reported.

DR. BUCHER: Can I make a comment?

DR. GALLO: Yes.

DR. BUCHER: The -- the statement in the

report says that fluoride is added to water at one part per million (1 ppm) which is considered optimal for the prevention of dental caries.

Right now that is a factual statement, that's the position that --

DR. LEE: (Interposing) Well, it's not factual in the sense they're optimally referred to as de- -- defined in 1943 when there were no other sources of fluoride intake.

So, you either have to say the definition has changed or -- or it was wrong in 1943.

DR. GALLO: We appreciate that.

We -- we'll work on that one.

Thank you.

Oh, I'm sorry. Doctor Silbergeld?

DR. SILBERGELD: This is perhaps more a question to the NTP provoked by the comment that was made.

Going back to this issue of the interactions with viral exposure suggested by Proctor and Gamble, are there any comments that can be made on the basis of the sentinel animal program described in this volume as to whether or not a similar event may or may not have occurred in this population?

DR. BUCHER: Well, we had -- we did the serological analyses on our sentinel animals throughout the study and found no indication of any disease state at all in our animals.

So, I don't --- I don't know enough about the virus that has been described in the Proctor and Gamble study to indicate to you whether it was included in our program or not.

DR. GALLO: I'd like to just table that one for now.

Doctor Tennant who was the expert in that area, I don't even know if he is in the room, with a crowd like this, it's kind of tough to see, but I'll try and call him at lunch and we can answer that question.

DR. GALLO: Thank you.

Doctor Lee, thank you very much.

The next speaker is Doctor Melvin Reuber from the Safewater Foundation, Delaware-Ohio.

Doctor Reuber?

(Doctor Reuber comes to podium.)

DR. REUBER: Thank you, Doctor, ladies and gentlemen.

I would like to comment about some of the rare

tumors that occurred in these studies.

The neoplasms of the liver that have been called hepatoblastomas, and hepatocholangiocarcinomas by others, are, by whatever name you call them, rare and unusual tumors.

I first described this lesion or tumor in mice in Doctor Hissen's laboratory at the National Cancer Institute with a viable yellow g.

The diagnosis that I used and the areas that were agreed with was party differentiation of cholangiocarcinomas.

The lesion was rare. We observed it in -- the first time in ten mice out of thousands and thousands of mice of many different strains.

Later, it was published -- I published this in the Journal of the National Cancer Institute in 1967.

Later, the same lesion was reviewed and published in hepatoblastoma, but as I said it really doesn't make any difference what you call it.

I suggested that since Doctor Hissen was taking one section of one tumor per mouse, that

if he would take more sections we might find more tumors.

And as soon as he started taking a section from every liver tumor, the number that we found went way up.

However, it was still confined to -- to mice with the probably -- the yellow -- they may occur but I have never seen them in other strains or in this strain.

I think -- you know -- it's safe to say that I've seen more of these than anybody in the world.

And secondly the osteogenic sarcomas of the bone, it's another rare neoplasm, has been pointed out; you can find metastases for microscopic tumors.

And there was metastasis from a tumor that was not observed grossly.

I've even seen metastatic osteogenic sarcomas when there was a microscopic primary in the tail.

Much has been made about the preneoplastic lesions of the bone.

In the working groups of -- pathology working groups of view, they pointed out that the osteosclerosis is seen in studies in which animals

were given radioisotopes and was indeed considered preneoplastic.

So, I -- I -- from my point of view the ostesclerosis might well be preneoplastic.

The fibrous osteodystrophy is dismissed because of the chronic renal disease. However, animals with these lesions have parathyroid hyperplasia, and if there were parathyroid hyperplasia described, I've missed it.

As far as the squamous cell carcinomas, the squamous epithelium of the oral mucosa and other organs, I think dysplasia is a precancerous lesion and that it's important to distinguish between dysplasia and degeneration.

To make this argument stronger, there were squamous cell carcinomas of the zymbolus gland, capillary angiomas to the skin and nasal cavity.

In my experience with diethylnitrosomines nasal cavity carcinomas are often microscopic, and again, it's a matter of looking for them.

Another target organ is the kidney, and I think that these lesions in the kidney have not been adequately analyzed, because the controls get mild lesions and the treated animals get severe

lesions.

Then, if I may comment on the striking discrepancies in the diagnoses between the study pathologists and the experimental pathology laboratory.

Liver adenomas in mice and rats were downgraded from adenomas to foci.

Apparently, based on nothing more than how much compression there was. If you take a second section someplace else you will probably find compression.

Also adrenal corticoneoplasms were changed from -- to hyperplasias, adrenal metathane neoplasms were changed to hyperplasia.

Dentine dysplasia was changed to degeneration.

I just -- I -- I could have expected some disagreements like this twenty (20) years ago, but I think that -- that today we should have progressed beyond that point.

There are a lot of comments that I'd like to make about the -- that are -- that are made in the final draft report about the osteogenic sarcomas. However, I -- I don't think I have the time.

I would just say that I can't remark or

evaluate results of unpublished studies that are not made available to the public and that are considered trade secrets.

Thank you.

DR. GALLO: Wonderful. You have two minutes. Okay.

Any questions from the Panel?

Thank you very much.

I'll turn the alarm off.

Doctor Goodman.

DR. GOODMAN: You indicated that in your view, osteosclerosis might be considered as a precancerous lesion.

DR. REUBER: Yes.

DR. GOODMAN: In these particular studies the clearest evidence of osteosclerosis was in the female rats that had no osteosarcomas while there were a few osteosarcomas in the male rats.

In light of what you said, then, could I not consider the bone tumors in the male rats as simply spurious?

DR. REUBER: No, not at all.

I mean, who knows whether the female rats had lived another six months whether they would have

tumors.

I mean, --

DR. GOODMAN: No, my point is then why would the -- if what you're saying is correct, why do we not see evidence of after osteosclerosis in the male rats that developed the tumors?

DR. GALLO: If it's a precursor lesion.

DR. GOODMAN: If it's a precursor lesion, thank you.

DR. REUBER: Well -- you know -- from reading the report, I can't answer that.

DR. GALLO: Any other comments?

Doctor Eustis? Doctor Bucher any comments? None?

Thank you very much, sir.

The next speaker -- oh, I'm sorry.

I'll chastise myself in a moment.

The next speaker is Gary Whitford from the Medical College of Georgia, Augusta, Georgia.

(Doctor Whitford comes to podium.)

DOCTOR WHITFORD: Thank you.

I'm Gary Whitford from the Medical College of Georgia. I'm a Regents' Professor of Oral Biology.

I received my Ph.D. degree in toxicology from

the University of Rochester and my dental degree from the Medical College of Georgia.

I've been actively involved in research on the metabolism toxicity of fluoride for about twenty (20) years. I'm here as an interested scientist, and I appreciate the opportunity to make comments.

First, I draw your attention to certain statements in the technical report which could be modified for the sake of greater accuracy.

Examples are the paragraph which begins at the bottom of page seventeen (17) and the second paragraph on page ninety-two (92).

On page seventeen (17) it is said that, quote, "In summary sodium fluoride is mutagenic in cultured mammalian cells and produces transformation of SHE cells in vitro", close quote.

I believe that statements like this should give some indication of the doses used in order to avoid alarming readers who are not familiar with the literature.

While the results of some studies support the statement, fluoride concentrations used are higher, usually several -- several orders of magnitude higher than those which can occur within the human

body.

The inclusion of a qualifying phrase such as quote, "at concentrations much higher those which occur in humans...", close quote, would convey the message more accurately.

It might be argued that bone fluoride concentrations reached levels that might be cytotoxic in some way or another.

This was done on page ninety-one (91) of the report where the possible link between fluoride concentrations and osteosarcoma is discussed.

However, it is known that the fluoride of bone is accumulated in the mineral phase and not in the aqueous phase. While there are no data to indicate the precise levels in or around bone cells in vivo, it is a virtual certainty that they are many times lower than those of the mineral phase.

Therefore, attempts to draw conclusions about the fluoride levels in bone cells based on the levels in whole bone are highly speculative.

Now, I'd like to summarize the pertinent findings from a recently completed GLP chronic toxicity study with Sprague-Dawley rats.

In this study, fluoride was administered in the form of dentifrices. The experimental design is shown on the first slide.

(Projecting slide.)

DR. GALLO: Doctor Whitford you're going to have to work the lights from up there, sir.

DR. WHITFORD: Okay. Someone told me how to do that but let's see if I can figure it out, the right three switches?

DR. GALLO: There you go. Slide them down.

DR. WHITFORD: Okay.

DR. GALLO: There you go.

DR. WHITFORD: There were six (6) groups in a a total three hundred and sixty (360) rats. The fluoride doses ranged from zero to twelve point five (12.5) milligrams per kilogram per day.

The doses were given once each day, seven days per week, for eighteen (18) months. There were interim sacrifices at six and twelve (6-12) months.

As was done in the NTP study, urinalysis, serum chemistries, and hematologic evaluations were done routinely.

With the exception of the twelve point five

milligarms per kilogram group, there were no differences among the groups for these determinations.

The twelve point five milligram per kilogram (12.5 mg/kg) dose proved to be too high.

The male and female rats died usually in renal failure between the sixth and twelfth months.

(Projecting slide.)

This slide, shows the tissues that were examined histologically. Femur was the only bone examined. Of all the tissues shown here -- all of the tissues shown here were examined in the saline control group, and the twelve point five milligrams per kilogram (12.5 mg/kg) group.

Kidney, stomach, liver and bone from all rats were examined.

The only abnormalities of bone were noted in the male rats sacrificed at eighteen (18) months. These abnormalities were occasional, small demineralized areas appearing in the cystic structures in the compact bone of the diaphyses.

In the saline control group, only one rat showed these structures.

In the fluoride-dosed groups, the frequency

ranged from thirty percent (30%) to fifty percent (50%).

There was also evidence of trabecular thinning among the rats sacrificed at eighteen (18) months, but it occurred about equally in all groups.

There was no evidence of osteosarcoma or any other bone disorder.

In a few rats, benign tumors such as fibroadenoma, tubular adenoma and cystadenoma were present. It was the pathologist's opinion that these probably originated from the mammary gland.

There was no correlation of these benign tumors with the administration of fluoride.

One female rat in the two point five milligram per kilogram (2.5 mg/kg), twelve month group had a subcutaneous carcinoma of the skin adnexa.

One male rat in the point two five milligram per kilogram (.25 mg/kg), eighteen (18) month group had a metastatic adenocarcinoma in the liver and abdominal cavity.

Other than that, no evidence of carcinogenesis was found in these two groups. There was no evidence of carcinogenesis in the twelve point five milligram per kilogram (12.5 mg/kg) group.

It was concluded that the administration of point two five (.25) or two point five (2.5) milligrams F per kilogram (2.5 mg F/kg) for eighteen (18) months caused consistent evidence of toxicity of any kind that distinguished these groups from the control groups.

I would comment briefly about the interpretation of the bone cancer findings in the NTP study. As discussed in the technical report, the study differed in several important ways from those done previously at NTP.

Unlike prior studies in which only one or two kinds of bones were examined, the present study examined eight different kinds of bones.

Three of the four cases of osteosarcoma originating in bone occurred in vertebrae.

As I understand the report, this type of bone has not been examined in previous studies.

Thus, there are no historical data to indicate the overall frequency, nor, what is more -- probably more important the expected variability among control groups for this lesion.

Historically, the frequency of osteosarcoma in other bones has ranged from zero to six percent

(0.6%), with no apparent explanation other biologic variability.

The distribution of osteosarcoma in the present study could have been due to the same kind of variability.

In view of this as well as the negative findings from -- from other studies, it seems to me that the Panel would be justified in setting aside the preliminary conclusion of equivocal evidence and judge the study to be inadequate because of, quote, "major qualitative or quantitative limitations", close quote; that is, the lack of an historical data base with particular reference to car- -- cancer in vertebrae.

Thank you.

DR. GALLO: I was about to tell you you had about twenty (20) seconds.

Thank you.

Will you put the lights back up for us?

We work enough in the dark.

Questions from the Panel?

Doctor Carlson?

DR. CARLSON: Yeah. I'm not sure about other studies. In other words, we don't really put aside

other studies. We try and judge -- we're supposed to judge the document as written.

DR. GALLO: That's correct.

DR. CARLSON: Obviously, we take into account strange things, or we look in places where things have been shown in other studies.

My question, though, has to do with, if you had -- if the same type of tumor had occurred, these osteosarcomas of the vertebral bones, would you have found these based on your protocol, since you only looked at the femur?

Whitford. No, no. That's right, we couldn't possibly - see, at the time this study was initiated there was no indication -- there was no reason to look at a large variety of bones, at least in our -- our view at that time. There is now.

DR. GALLO: If I'm -- go ahead, I'll ask the question later.

DR. McKNIGHT: I just have a quick comment on that, and that is, not only were the tumors not looked for as carefully in your study but also because of the shorter length and the much smaller sample sizes in the different treatment groups, your study had considerably less sensitivity.

DR. WHITFORD: I fully agree with that, right.

But since I had the data and it seemed pertinent, I thought I'd offer you that.

DR. GALLO: We appreciate that very much.

DR. WHITFORD: Yes.

DR. GALLO: One question is, in your laboratory, what information do you have on your own historical controls, and I'm not casting a stone, I'm just asking.

DR. WHITFORD: Sure, yeah.

And I'll tell you the truth. I -- we have none. This is the -- the first thing --

DR. GALLO: (Interposing) First shot.

DR. WHITFORD: -- of this type that I've ever done.

DR. GALLO: Thank you.

Are there any other questions?

Yes, sir, Doctor Hayden.

DR. HAYDEN: I'm just wondering, if I read our report correctly, if the gross evaluation of previous historic controls is not comparable -- I mean is comparable, because all of the vertebral tumors observed in the study, if I read it right, were observed grossly.

DR. WHITFORD: That's correct.

DR. HAYDEN: So, there were none that were detected by radiographic examination, therefore, there should be some comparability there.

There was, however, one tumor in a long bone that was detected only by microscopic examination.

DR. GALLO: Is that the end of your response? John?

DR. BUCHER: I'd just wanted to mention that several times it's been stated that the -- the tumors that were observed grossly were not seen radiographically. In fact, they all were seen radiographically but they were also picked up grossly.

I didn't want to leave that point of confusion.

DR. GOLD: But the point -- excuse me.

But the point here is that they would have been picked up ten -- five years ago in a gross exam the same way. This study wasn't peculiar in that respect.

DR. GALLO: That's correct.

DR. BUCHER: I think that's probably correct.

DR. GALLO: Okay. Thank you.

We're moving along, we're going to make it, I think.

DR. SILBERGELD: Wait, I --

DR. GALLO: Oh, I'm sorry.

Speak up, Doctor Silbergeld.

DR. SILBERGELD: I'm sorry. If I might have the mic?

Did you do any examinations that might speak to these oral cavity lesions that were noted in this study that might help us put those in some kind of context?

Whitford:

No, not -- not in this study.

We -- we have done two thirty (30) day irritations and wound healing studies with topical applications that there were really no known -- no signs of cancer but they were relatively limited studies in terms of times.

And doses were extremely but a short time.

DR. GALLO: Any other comments?

(No response.)

Thank you, Doctor Whitford, appreciate it.

Our next speaker is Doctor John Stamm from the University of North Carolina Dental Association.

Doctor Stamm?

(Doctor Stamm comes to podium.)

DR. STAMM: Thank you, Mr. Chairman.

Before the clock ticks -- is it ticking?

DR. GALLO: Go ahead, I'll hold it.

DR. STAMM: I'm speaking for the American Dental Association. There is no UNC Dental Association.

DR. GALLO: Okay.

DR. STAMM: So, I'm the spokesperson for the American Dental Association.

The American Dental Association is deeply interested in the -- if I can get the first slide, please --

(Projecting slide.)

DR. STAMM: -- is deeply interested in the information contained in the National Toxicology Program's technical report.

In the report, the NTP concludes that under the conditions of the two-year dose water studies, there was equivocal evidence of carcinogenic activity, sodium fluoride in male rats.

The American Dental Association believes that the NTP's interpretation is not justified based on four considerations.

First, the criteria used by the NTP to assess strength of experimental evidence in the fluoride study appeared to depart from norms used by NTP and NCI over many years.

Second, the NTP interpretation appears to have given insufficient attention to the relative contributions of increased and decreased incidence of tumors in rats.

Third, there is a recent suggestion that some NIEHS investigators themselves may regard compounds categorized as equivocal by NTP to be more properly seen as noncarcinogenic.

Fourth, extensive epidemiological studies on humans have consistently shown no link between water fluoridation and cancer.

Only the first and fourth issues are addressed below. Our written summation contains greater and additional details.

(Projecting slide.)

first, have the criteria for evidence changed?

Examine table one and notice three particular features in the data, the crude rates for osteosarcoma in the three treatment groups, two percent (2%) in the hundred ppm (100 ppm) group,

three point seventy-five percent (3.75%) in the hundred and seventy-five ppm (175 ppm) group.

Notice, secondly, that in all the pair-wise comparisons of the treatment groups to the control, no statistical significance was observed.

Finally, that the statistical analysis revealed statistical significance only in the trend analysis.

Consider table two, abstracted from a 1982 NTP study which used virtually the identical protocol to assay stannous chloride.

It is evident in comparing table one with table two that the latter showed stronger, statistically significant dose-response trends and incident differences for more tissue types and more species sex specific groups.

Interestingly, for osteosarcoma, the crude rates were two percent (2%) and four percent (4%).

Yet, the NTP judged stannous chloride not to be carcinogenic.

The American Dental Association notes with concern an apparent inconsistency in categorizing the results of two similar carcogen- -- carcinogenicity studies.

In seeking to determine if the NTP may have altered its criteria for evaluating the strength of experimental evidence, two possible departures from former practice are cited.

One, in 1977, the NCI Carcinogenesis Bioassay Program, the predecessor to the NTP, used the following statistical guideline to define tumorgencity: quote, "For tissues with spontaneous tumor rates greater than two percent (2%) we classify a chemical as a tumorigen if we observe a significant tumor increase at both dose levels, i.e., moderate and high.

For the remaining tissues, which have low spontaneous tumor rates, we will classify a chemical as a tumorigen if we observe a signficant tumor increase at either dose level.

If these same criteria are applied to table one, the sodium fluoride table, the lack of statistical significance for any of the pair-wise -- pair-wise comparisons would clear sodium chloride as a carcinogen.

Two, from table one it was seen that the only statistical procedure to indict sodium fluoride was a trend test. However, in a recent report, it was

shown that the sole reliance on the trend test classified sixty-three percent (63%) more compounds as carcinogenic than the historical NCI/NTP procedures.

This led NTP personnel to declare at that time that, quote, since the proportion of compounds actually labeled as carcinogenic by -- by NCI/NTP is far less than that indicated by the significant trend decision rule. This clearly demonstrates that one must adopt an even more conservative approach to obtain an accurate approximation of the actual false/positive rates for NCI/NTP bioassays.

The American Dental Association agrees with this position and is concerned that such a policy appears not to have been factored adequately into the decision process for the sodium fluoride study.

Now, to the matter of does fluoridation increase risks of cancer in humans? There have been numerous technically sound epidemiological investigations into the possible relationship between fluoridation and cancer.

None of these have uncoverered significant increase in human cancer incidence or mortality.

Representative of these investigations is a

study by Doll and Kinlen by which the data in table five here are reproduced. Using standardized mortality rates for the U.S., the authors compared observed with expected cancer deaths in fluoridated and nonfluoridated cities.

Comparisons were included for periods before and after fluoridation.

The ratio of the observed and expected numbers fell slightly for the communities that fluoridated and remained virtually unchanged for the nonfluoridated communities.

This led Doll and Kinlen to state that, quote, "The American evidence when analysed in detail is consistent with the British evidence that was examined earlier by one of us.

None of it provides any reason to suppose that fluoridation is associated with an increase in cancer mortality, let alone causes it."

DR. GALLO: About forty-five (45) seconds, sir.

DR. STAMM: Thank you.

With specific reference to bone cancer, the extensive investigation has been carried out by Hoover, et al. at The National Cancer Institute.

Again, observed mortality cases were compared to expected cases and the appropriate ratios were calculated.

That's it.

Table -- table six shows that these ratios demonstrates no change in bone cancer mortality took place within fifteen (15) years after the implimentation of water fluoridation.

In conclusion, the American Dental Association appreciates the opportunity to comment on the NTP sodium fluoride study.

However, based on extensive studies from large-scale human experiments and based on several significant reservations, concerning the interpretation of evidence in the NTP animal study, the Americal Dental Association believes that carcinogenicity of sodium fluoride has not been demonstrated.

The Association is deeply concerned that, if left unaltered, the conclusion from the NTP study will be used fto formulate completely inappropriate inferences concerning the cancer risks as- -- associated with water fluoridation throughout the world.

Thank you very much.

DR. GALLO: Thank you.

Would you mind putting the lights back up for us?

Thank you very much, Doctor Stamm.

Questions?

Doctor Goodman?

DR. GOODMAN: Comment and question.

Thank you very much for that clear presentation.

And the question is, could the chairman please provide us perhaps at lunchtime with a copy of this "Fundamental and Applied Toxicology" paper which was referenced, the one that's volume three, page --

DR. GALLO: (Interposing) Wait a minute.

I'll pull it out of thin air. Joe has it. Doctor Haseman has it. Actually, I'd like Doctor Haseman to respond to some of the --

DR. HASEMAN: Well, I would like to reassure the Panel that the statistical and other evaluative criteria used in the sodium fluoride study is not changed, it's the same that has been used at previous studies.

I'd like to commment briefly on the supposed rule that the NCI used which was taken from a brief communication by Fears and Tarone, a two-page response to a letter dealing with false/positive issues.

Nowhere in that article did they claim that this was the approach used by the NCI.

In fact, when I talked to Doctor Tarone, one of the authors yesterday, he was quite dismayed and surprised to learn that this was being attributed to the NCI, so that approach where you would, for example, require significant effects at both doses no matter how strongly affected the high dose for a common tumor, before you call something positive which is clearly not used.

In terms of the NTP, there was -- also, since that -- the evaluative approach allegedly used by the NTP referred to a paper of mine which, in another context, we discussed a possible approach that would evaluate a chemical as a carcinogen if a high dose -- if the high dose produced an effect for a common tumor that was significant at the one percent (1%) level or for a rare tumor was significant at the five percent (5%)

level.

Both in that paper and in several papers since then, we've re-emphasized over and over again that we did not use that roll, that this evaluation of long-term rodent studies is much more complex than that and takes into account many other biological factors.

But even if we used it, even if we had, in the sodium fluoride study, the interpretation is totally consistent with that approach because we do not interpret that as positive. We interpret it as equivocal, that the high dose effect was not significant, the trend was, and we interpret that as equivocal which is totally consistent with -- with that rule.

And the force -- I don't know whether to go into the four stannous chloride studies, those, too, were all misleading in that one of them was interpreted as equivocal, they were interpretted as negative. None of them would have been interpreted positive, had this so-called rule been employed, so once again, there is no inconsistency.

All these studies are interpreted correctly.

And finally I feel certain that if we were to

use inconsistent criteria, the Panel here would certainly correct that. So there are certain checks built into that in any case.

(Laughter.)

DR. GALLO: Again, I do want to thank you, Doctor Stamm, for bringing that out to allow Doctor Haseman to bring those two comparisons back up for us.

Thank you very much, sir.

DR. STAMM: I would just add that I -- in the more detailed report that we submitted was very careful to state that I thought the statistical work in this report was excellently done.

And furthermore I have no reservations about the procedures that were used. There are no changes from former procedures, in fact, the reports over the years are really very consistent.

The difference that I have with the -- is only with the interpretation of the analyses, and I do believe that the criteria for the sodium fluoride study appeared to be rather more stenuous than I think they have been in previous studies based on the types of evidence that I've submitted here for you.

DR. GALLO: There may also be a process of evolution there, sir.

I can't speak to it, but I think that's a part of this.

John?

DR. ASHBY: I'd like to ask Doctor Haseman about those osteosarcomas in stannous chloride. I know we don't want to get on to that study.

DR. GALLO: No.

DR. ASHBY: I know, but is that the one that you said was called equivocal?

DR. HASEMAN: That was -- that particular response was not the one equivocal. The C cell thyroid tumors were the one that was called equivocal.

That particular one was not significant by a trend test, was not significant by a pair-wise comparison, a low response, they all occurred in different sites. It was interpreted as -- as no evidence.

DR. GALLO: Thank you. Doctor Gold?

DR. GOLD: I would like to clarify the test for the Panel for the purpose of the rest of the people at the meeting.

We are charged with evaluating levels of evidence which appear on page four of the report.

There are five categories of carcinogenic activity.

These have been put into effect as of March 1986, and so things -- these categories -- equivocal did not exist as a category prior to that time.

Two categories are for positive results. Those are clear evidence and some evidence.

One category for uncertain findings, equivocal evidence.

One category for no observable effects, no evidence, and one for experiments that cannot be evaluated because of major flaws, inadequate study.

And equivocal evidence is further defined as carcinogenic activity demonstrated by studies that are interpreted by showing a marginal increase of neoplasms that may be chemically related.

The definition, as I read it, has two categories for postive results, clear and some. And the category "equivocal" is not included in that group.

DR. GALLO: Thank you.

Took my job away from me. That's okay.

Our next speaker is Doctor Edward Remmers, The American Council on Science.

Doctor Remmers?

(Doctor Remmers comes to podium.)

DR. REMMERS: Thank you, Doctor Gallo.

I'm Edward Remmers, vice president of the American Council on Science and Health.

The American Council is a nonprofit, title 1C3 Consumer Education Association that publishes very extensively on chemicals both manmade and naturally occurring in our air, water, soil and food supply.

They receive our scientific direction from a distinguished board of over two hundred (200) scientists and physicians.

The American Council is perhaps best known, at least recently, as the only scientific group to stand up and declare the recent LR apple scare to be a hoax and a fraud perpetrated against the American public since only a small number of rodents displayed the pathological condition at very massive doses.

On Tuesday of this week, the American Council held a press conference in Washington, D.C. to

present our pro-fluoridation position for drinking water.

We endorse the scientific positions of the other pro-fluoridation speakers at today's presentation here.

Today, I ask the NTP Board of Scientific Counselors to do two things. First, acknowledge that high dose rodent studies simply are not infalible predictors of cancer risks in humans.

And two, reject the recommendation of those who allege that the EPA should classify fluoride as a probable human carcinogen and ban water fluoridation.

In the event that a governmental body or regulatory agency threatens the continued use of drinking water fluoridation and undermines public confidence, and its safety, we at the American Council wish to consider pursuing legal action.

We base our position on some recent cases where our legal system is now taking the position that human exposure studies, where they exist, and especially those of a long duration, vastly outweigh and overshadow all other types of evidence such as chemical, in vitro and laboratory animal

studies.

We commend our legal system for re-enforcing this key principle.

Page nineteen (19) of the NTP -- NTP draft technical report states that human exposure studies in six countries have failed to show an association between cancer mortality in human and the fluoride content of drinking water.

The international agency for research on cancer, IARC, concluded a review in March of 1987 that no human exposure studies have provided any evidence that an increased level of fluoride in water was associated with an increase in cancer mortality.

When we applied the logic that our legal system is more recently using, the fluoridated drinking water, we conclude fluoridated drinking water is safe.

We feel that the toxicology study of sodium fluoride represents good science, but bad extrapolations from rodents in humans.

In closing, we at the American Council are deeply concerned that the inappropriate use and improper interpretation of laboratory animal

studies cause public perception and the regulatory process to reject beneficial chemicals.

We plan a press conference in the fall of 1990 on the limits of extrapolating cancer risks from animals to humans, and possibly seeking Congressional redress of the increase in misuse of animal studies to needlessly terrify the American consumer about safe technologies and products.

Finally, we at the American Council urges our regulatory agencies to abandon the knee jerk reaction of classifying a chemal- -- chemical as a probable human carcinogen based on only limited animal data.

Thank you.

DR. GALLO: Thank you, Doctor Remmers.

I'd just like -- I'll address that from the chair.

As I said to Doctor Lee, I think you've made a -- and this may sound confrontational, I think you've crossed the line between risk management, risk extrapolation, and hazard evaluation.

I think you should -- I had asked that the comments be directed at the study, and I think this was a much different type of statement.

The question of toxicology is what we do here; extrapolation is not our job. And many of us will be involved in the extrapolation process I'm certain and many are involved in others. But again, those are two separate processes. The purpose of animal studies is to define a potential for a hazard.

I don't particularly ascribe to Alexander Pope of three hundred fifty or three hundred sixty (350-360) years ago, that the best study of man is man, particularly when we are studying, perhaps, experimental compounds.

I -- I personally take offense to the idea that -- that we -- your idea that we don't need animals to extrapolate to man. I think we do. I don't know of anybody that would want a new drug for instance, or some of these food additives put into our supply before it's gone into an animal.

DR. REMMERS: We actually defend the use of laboratory animals, and, in fact, will have a booklet out at the same time as the update of this booklet that the late Doctor William Abner wrote for us, Of Mice and Men: The Benefits and Limitations of Animal Cancer Tests.

DR. GALLO: Any comments?

Gary?

DR. CARLSON: Yeah, I also take a front that my scientific judgment should be swayed by the threat of a lawsuit, that this may be a legal thing that --

DR. REMMERS; Yes, it is.

DR. CARLSON: -- that bothers me.

DR. GALLO: Our scientist's judgment is a threat of a lawsuit? Is that what --

DR. REMMERS: It threatened by the lawsuit, yes.

If we decide the wrong way --

DR. GALLO: Sobeit.

Any other comments?

(No response.)

Okay. I have twenty-six (26) minutes after. Twenty-seven (27). We're on schedule, as far as I know, and let's take at that break for lunch.

The Panel will -- hold it -- hang on, don't leave.

DR. HART: the Panel ordered put in an order for a box lunch. There is a table in the cafeteria --

DR. GALLO: That's not working.

DR. HART: There is a table in the cafeteria -- can you hear me?

DR. GALLO: I can, but I don't think -- the Panel -- the Panel will eat together. There is a table set out for us. It's going to be a long line there. We have our box lunches, and they're there.

I also want to thank all the commenters. I think it was instructional to all of us, and we'll be back one thirty (1:30), sharp.

Thank you.

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(LUNCH BREAK, 12:30- 1:30 P. M.)

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DR. GALLO: Like to call the session to order, please.

Before we start the proceedings of the afternoon, which will be to decide on the levels of evidence by the normal procedures of the Panel, I have two letters that I would like to read into the record, and they will be put in the archives.

The first letter is from Dr. James A. Popp, D.V.M., Ph.D., head of the Department of Experimental Pathology and Toxicology at CIIT, and

this is a letter that's self-explanatory in response to one of the comments that we've had.

"Dear Doctor Hart: I recently became aware that a quote attributed to me is included in a prepared statement to be presented to the NTP Technical Reports Review Committee.

The attributed statement is relative to the NTP Technical Report on the Toxicology and Carcinogenesis Studies of Sodium Fluoride.

Testimony apparently prepared by Susan Pare on letterhead of -- from the Center for Health Action states that I have expressed to a, quote, 'reliab: source', unquote, that evidence linking fluoride to osteosarcomas in rats is quote, 'clear', unquote.

To assure the accuracy of information provided to the Review Panel, the following brief comment is provided. I do not recall commenting to anyone that I considered the results of the sodium fluoride study to indicate, quote, 'clear evidence of carcinogenic activity', unquote.

As a member of the Pathology Working Group I concurred with the diagnosis of osteosarcoma for several lesions presented to this group since the lesions clearly fulfilled the criteria for this

diagnosis.

The Pathology Working Group did not have access to the complete information package as provided in the Draft Report that is currently under review by the Technical Reports Review Subcomittee.

Without complete information, I believe it is impossible for me or any other member of the Pathology Working Group to make a determination of the appropriate level of evidence assignment for the sodium fluoride study.

If consistent with NTP policy, please make this statement available to the Panel and include it in the public records.

Sincerely, James A. Popp", dated April 25th.

That's one letter.

The second is from Doctor Curtis Klaassen who is a member of this Panel but could not be with us, and asked me to read -- or asked Doctor Hart to enter this statement into the record on the sodium fluoride study.

"Deart Doctor Hart: As a member of the NTP ad hoc subcommittee panel of experts, I am truly sorry but it is impossible for me to attend your meeting

during the last week in April.

This is the week of the year that I have taught the Mid-America Toxicology course in Kansas City for the last ten years.

I have read the 'Toxicology and Carcinogenesis Studies of Sodium Fluoride' and have a few comments. My points deal with the interpretation of the osteosarcomas in male mice."

DR. GOLD: He meant rats.

DR. GALLO: I think he means rats, that's right.

My -- my main concern -- that happens in Kansas City.

(Laughter)

"My -- my -- my main concern is with the second paragraph on page two, this paragraph -- that is the paragraph that abstracts the interpretation of osteosarcomas observed in male rats."

Now, he's got it.

"As -- as noted in the table on page A-54 two percent of the intermediate-dosed rats and four percent (4%) of the high-dosed rats were diagnosed to have osteosarcomas.

Also noted in that table is that this incidence is not statistically different from controls by pairwise comparisons.

However, the table also indicates that the trend test is statistically significant.

Page A-61 indicates that the historical incidence of osteosarcomas in these male rats is zero point five percent (0.5%) with a range from zero to six percent (0-6%).

These apparently are the facts, and I have no reason to dispute them. However, I do not think the second paragraph on page two captures the essence of this data.

First of all, I think this paragraph should indicate not only the mean of the historical controls; that is, zero point five percent (0.5%), but also the range, zero to six percent (0-6%).

Secondly, this summary states that the osteosarcomas occurred with a statistically significant dose response trend, but no indication is given that the treated groups are not statistically significant from the controls.

These points are essential in the abstract if one desires to give an unbiased interpretation of

the data.

Since you are in North Carolina, I will provide you with an appropriate statistical analogy.

In 1988 the University of Kansas defeated Duke in the first game of the NCAA final four basketball tournament. Thus one can conclude that Duke was number three or number four in the nation in 1988.

In 1990 -- in 1990, Duke was defeated by UNLV in the first game of the NCAA tournament. Thus one can conclude that Duke was number two in the nation..." -- in the final game, excuse me -- "number two in the nation in 1990. Statistically, one could perform a trend test and conclude that Duke has a statistically significant trend to be number one basketball team in the United States.

(Laughter.)

But they are not number one."

(Laughter.)

DR. RALL: No, but that will be next year.

DR. GALLO: That's next year, right.

DR. RALL: And the local people agree with it wholeheartedly.

DR. GALLO: "Similarly, while there might be a

trend for fluoride to increase osteosarcomas, it didn't. The abstract needs -- need to state that.

Sincerely, Curtis Klaassen."

And I'm not going to comment on Rutgers.

(Laughter.)

Okay. The business at hand is to address the questions of level of evidence.

Are there any further questions or comments from the Panel?

Doctor Gold?

DOCTOR GOLD: The Proctor and Gamble study made me want to make sure we get into the text the fact that the dosing schedule in the NTP bioassay uses a constant ppm in water and therefore, at the time that bones are developing in young animals, the dose of fluoride is actually higher because they drink a larger proportion of their body weight.

DR. GALLO: Thank you. Okay. Anything else?

Doctor Zeise?

DR. ZEISE: I wanted to look very briefly at dose selection in the study.

If we look at the six-month study, on which the dose selection was based, and then the two-year

study, it's not quite clear to me that the animals couldn't have withstood higher doses and particularly for the -- for the female mouse.

I was wondering if we could go over that.

We didn't see any decrements in body weight or changes in survival in the study.

The question is; could we have gone higher.

If we look at the six-month study for the female mouse, anyway, it looks -- all the animals survived, and it doesn't -- it appears -- it's not quite clear to me why the lower dose was selected for the female mouse.

DR. GALLO: Thank you.

DR. BUCHER: Well, I think the dose selection was based on the body weight changes that were seen in the animals given two hundred parts per million (200 ppm) at higher concentrations.

The -- in fact, it was consistent in males and females, and I don't think that at the time it was considered appropriate to select different doses for the females and the male mice.

DR. ZEISE: Do you think they could have withstood higher doses, --

DR. BUCHER: (Interposing) I think --

DR. ZEISE: -- if they had ordered maybe three hundred ppm (300 ppm) in females than in males?

DR. BUCHER: Well, I don't know that -- that we have enough evidence to -- to state that males and females were that much different.

We did lose one mouse at three hundred parts per million (300 ppm) in the male group.

They could probably have tolerated somewhat more than a hundred seventy-five parts per million (175 ppm), but I don't know how closely we can titrate a dose. I really can't predict what would happen at a slightly higher dose.

DR. ZEISE: I'd like to ask the same question for the rats. Apparently the selection of dose was based on the finding of the ulcer in the height -- the male rat and in the female rat.

DR. BUCHER: And the weight effect.

DR. ZEISE: And the weight effect.

DR. BUCHER: Right.

DR. ZEISE: You -- if I look at the weight effect, I don't -- let me make sure I have the right table here. On page -- table three, page thirty-eight (38), I see for the female the weight

decrement is just about what we want after six months for an MTD, and for the males it's a little bit more than that.

DR. BUCHER: Well, if you consider both the ulcer that was seen in both the male and female, one mouse in the high dose group, and the weight effect, I think that we would not have chosen three hundred parts per million (300 ppm). We might have chosen -- again, we might have titrated the dose somewhat closer but how closely, I don't know.

DR. ZEISE: How life threatening were the ulcers in the hyperplasia?

DR. BUCHER: Well, the one --

DR. ZEISE: (Interposing) Is the rats?

DR. BUCHER: -- the one ulcer, and I believe it was a female, was a penetrating ulcer and there were multiple small ulcers in the male. I could probably -- should defer that question to Doctor Haseman or Doctor Eustis.

DR. EUSTIS: Certainly, a penetrating ulcer is life threatening, and I think you also have to consider the fact that the hyperplasia that was present -- present in the other animals is an

indication of gastric toxicity. It's an indication of increased self-turnover that's present, probably due to excess loss of cells from the mucosa.

So, I think taking that into consideration along with the fact that we have ulcers in -- in those animals and one was perforated, I think there is a potential problem if you go higher.

DR. ZEISE: So, from what I understand, it's just the female mouse that really possibly could have withstood a higher dose, comfortably.

DR. GRIESEMER: I think it important to emphasize that they could not have withstood a doubling of the dose that we used. We're talking about some relatively minor differences for which we don't have any better information.

DR. ZEISE: Thank you.

DR. GALLO: Would you -- Doctor Zeise, would you like to see a statement in -- somewhere in the text to that effect on the female mouse that -- that though we realize that they may not have been able to tolerate a doubling of the dose, that some increment of the one seventy-five (175) might have been tolerated?

DR. ZEISE: I think that would be helpful.

DR. GALLO: Okay. Thank you.

Okay. If there are no further comments -- or are there further comments? I'm sorry.

Doctor McKnight?

DR. McKNIGHT: I'd just like to make one more plea for including, if not in the primary analysis, perhaps in another appendix, to be added to the final version of statistical analysis based on including the paired controls on whom the complete pathology was performed in the control group.

Particularly, when the historical groups are not comporable, as they are in this setting, I think they give us more information about what the tumor incidences are in animals fed with this low fluoride diet.

DR. HASEMAN: How bad is a compromise including the analyses restricted to those tumors that matter like osteosarcoma, oral cavity, thyroid, and a few others, rather than add another hundred (100) or twenty (20) or thirty (30) or forty (40) pages of analyses on noneffects, would that be acceptable?

DR. McKNIGHT: It would.

DR. HASEMAN: I mean, I think we can do that.

DR. GALLO: Doctor Longnecker?

DR. LONGNECKER: I'd like to ask Doctor Eustis a question, and that is whether the lesion that's illustrated on plate two on page forty (40) is the same one that was referred to as oral squamous metaplasia by the study pathologists?

DR. EUSTIS: This was the acute lesion. In other words, this was seen in the animal at -- at six months.

The lesion referred to as squamous metaplasia was actually seen at the end of two years. However, I think the complicating factor here is that the -- as the layer of ameloblast fulfill -- fulfill their function of secreting enamel, they eventually become squamous cells as they progress towards the surface.

And as you have a degenerative process and you lose the ameloblast you're actually going to get the transition to squamous cells.

So, it's not -- it was a degenerative process involving the ameloblast and not a metaplastic reaction like you might find in the trachea of -- of a person smoking or something else.

DR. GALLO: Doctor Silbergeld?

DR. SILBERGELD: I would like to see some mention in the text, and I will be happy to provide references to the staff on the possible sex-related differences in mineral tissue metabolism which might go towards -- be noted in this finding of an incidence in only one sex.

DR. GALLO: Thank you.

Doctor Gold?

DR. GOLD: I have really a question.

So, from the control group that gets about point two milligrams per kilogram (.2 mg/kg) per day to the highest dose group that gets about four milligrams per kilogram (4 mg/kg) per day, we're going a range of twenty (20) fold in fluoride exposure.

I'm just -- I'm not clear what we're doing in this statistical and theoretical sense compared to what we usually do when we have a zero control group, so I think -- maybe I need some clarification, but certainly think we should say in the report that we are -- we are not judging the carcinogenic activity of fluoride against no fluoride. We're judging across a dose range of

twenty-fold.

DR. GALLO: It's nice to hear toxicology once in awhile.

In fact, we are going against the background. I don't -- I think with the clarifications that we -- we talked about this morning, we may need a -- a stronger sentence, declarative sentence to to that extent.

You know -- we have a test system, and under the conditions of the test system, these are our results and our conclusions.

And I think that from what I heard this morning and agreed upon by the staff, that there will be clarifying sentences in the document.

DR. ZEISE: Final question with respect to dose selection.

At what diet did the animals that received the treatment in the six month study, what diet did they receive. Did they receive the same diet as -- as the two-year study, or did their diets have more fluoride?

DR. BUCHER: The diet in the six-month study was a low fluoride semi-synthetic diet containing about two point one parts per million (2.1 ppm) of

fluoride, excuse me.

DR. GALLO: Thank you.

DR. GALLO: Any further question?

Okay. Based on the discussions this morning, I really heard several things around the table on level of evidence.

I heard some individuals suggest that there may be no evidence for carcinogenic activity and then on up from there.

Doctor Goodman, I believe, expressed the strongest sentiments for suggestion of no evidence, and I would like to give him the opportunity to make a motion on that, and I'll leave it at that.

DR. GOODMAN: I think that viewing the data in this report, to me there were four saline features. First, the question of comparison with historical controls, and I recognize here that in the historical controls we are dealing with higher levels of fluoride in the diet than with the present study.

But nevertheless, that considered the number of osteosarcomas seen in the high dose group was within the range of historical controls with the caveat I mentioned.

Second, the question of scrutiny of bone in the current study relative to previous studies, I think was important. And I'm talking about scrutiny in terms of microscopic examination and we could only wonder what did hap- -- what would have happened with historical controls if they had been scrutinized at this level.

And secondly, in terms of scrutizing bone to think of what has happened with other chemicals like nitrofurantoin that was mentioned before where there was even a higher level, perhaps, of osteosarcomas in dosed animals, but that was not viewed as -- as a very noteable.

Third, the question of fluoride accumulation, and here fluoride clearly accumulated in bone of male and female mice, as well as male and female rats.

Indeed in terms of osteosclerosis the highest level seen was in the female rat where no osteosarcomas were seen. And last that there was no statistical difference between the high dosed male rats and the controls in the current setting.

And I think that can lead to an interpretation of no chemically related tumors. And for that

reason I would make a motion for no evidence.

DR. GALLO: Thank you.

Do I have a second to that motion?

DR. DAVIS: Second.

DR. GALLO: Second.

Discussion among the Panel.

We'll start with -- always look to the left first, so go ahead.

DR. SILBERGELD: To my mind, the strongest argument militating against that, leaving aside the discussions that we've had about the statistical analyses, and the oral cavity findings, is the issue of target organ expression on effects.

It is very hard for me to discount entirely and come up with a conclusion of no evidence, which is a discounting entirely of all the signals that are present in this data, when, in fact, the tissue that's affected is the tissue that one would expect on all that we know about the biological actions and disposition of this compound to express a response.

DR. GALLO: Thank you. Doctor Gold, comment?

DR. GOLD: Is that really right; that is, there are other results that are sort of as strong,

but we've excused them for other reasons, like background?

DR. GALLO: The question you're asking is --

DR. GOLD: (Interposing) Is this really the target organ? It's the one we're interested in.

DR. GALLO: Well, Doctor Silbergeld is -- you approach data from two points, at least, I think that's what Claude Bernard said; one is observation, the other is hypothesis.

And what Doctor Silbergeld is saying is what I heard an awful lot this morning, that the hypothesis here, is that this is a target organ. What you're saying, however, is the observation, and is that observation pure chance?

And I think that's the question that we have to ask.

DR. SILBERGELD: Clearly -- but clearly, Lois, the toxic- -- leaving aside the findings of neoplastic and preneoplastic changes, the toxicology, I think clearly re-enforces the general assumption, that mineralized tissue is the target organ for fluoride.

DR. GOLD: That's true.

And we're looking very carefully for it, I

agree with that, but if the results on osteosarcoma are not necessarily greater than for some other sites but we -- we decided they weren't -- or the staff decided not to put them forward for other reasons.

And this one we're doing slightly more careful scrutiny of that very reason.

DR. GALLO: I think that's stated up front in the report, also. I mean, that's -- I mean, the approach taken in the report was the hypothesis avenue. They said, this is the target, let's go for it.

Bill?

DR. HASEMAN: Defending NTP call of equivocal, I would just like to point again, that this is an uncommon tumor, that just because one time out in a hundred and twenty-two (122) studies, we happen to have seen a control rate -- you know -- similar to this one does not negate the fact that I think being a target organ as was pointed out, and being a rare tumor that surely there -- I mean, in my judgment, surely at least that's equivocal.

And also don't forget the subcutaneous

osteosarcoma. I mean, it's not being pooled with the bone tumors but that's another little teeny bit of evidence that I think supports the fact that this is a marginal effect that may be chemically related, uncertain.

DR. GALLO: That's the word I think a lot of people would like to use.

DR. HASEMAN: That's what equivocal is.

DR. GALLO: That's exactly right.

Doctor McKnight, go ahead.

DR. McKNIGHT: Just the point that without inclusion of these paired controls, if anything of statistical significance, of the osteosarcoma findings, since there were none found in the paired controls, is slightly understated.

DR. GALLO: Any other comments from this side of the table?

(No response.)

DR. GALLO: Our primary reviewers?

John?

DR. ASHBY: As Doctor McKnight raised that point, what are the data on that? What is the p values for the trend of the top dose so that we'll know what is being discussed with the paired

controls?

DR. HASEMAN: My recollection is if we factor in the paired sacrificed control data, there were about forty (40) of them that -- that died relatively early, plus the interim sex, the two sets of interim sex, the trend based on the three bone cancers in the high dose, and the one in the middle dose.

The trend goes from on 027 -- p of 027 to a p of 106, and the high dose effect which was, I think, 099 becomes p of 067, still not significant at the five percent level.

So, that extra control data, if you accept that analysis will strengthen it a little bit. Not -- you know -- not greatly but strengthens it a little bit, because it factors in the absence of those tumors in the controls, in those additional controls.

DR. ASHBY: Okay, but it is under the trend because 067, is way off the significant trend.

DR. HASEMAN: 067 is the high dose effect. 016 is the --

DR. ASHBY: That's a long way away from normal significance, so it really is only the trend that

we're talking about.

DR. GALLO: I'd like to -- I'm sorry.

DR. LONGNECKER: To vote for the motion as made would mean that I had to be very comfortable with the idea that there are no questions left in my mind, and there are questions left and therefore I cannot be comfortable with that motion.

DR. GALLO: I think -- I think I'll call the vote, and then we'll see how it comes out. Okay. And then we'll go to the next one.

DR. HART: Do you have a second?

DR. GALLO: I have a second, --

DR. DAVIS: You have a second, but before you call for the vote, I'd like to -- for the sake of the audience what we said yesterday, that a motion might be made and seconded in order to move it along, --

DR. GALLO: (Interposing) That's correct.

DR. DAVIS: -- so, that if we don't --

DR. GALLO: (Interposing) You don't have to excuse your second.

DR. GOLD: Can I ask one more question?

DR. GALLO: You get one.

DR. GOLD: One more question and this is to

Doctor Haseman.

When you were raising the issue that there were once -- there once was an incidence of six percent (6%) or three out of fifty (50), same three that we're seeing here, only out of fifty (50) instead of eighty (80) in a -- in a control group that received something between the low and mid dose of this bioassay of fluoride?

DR. HASEMAN: Presumably, that's correct.

DR. GOLD: So, I don't know how to factor that information in. It isn't as if it were zero.

DR. HASEMAN: One study out of a hundred and twenty-two (122)?

DR. ALLABEN: That's not -- the point is they've gotten a lot of fluoride?

DR. GALLO: The fluoride is there.

DR. GOLD: Between the low and the mid dose?

DR. HASEMAN: That's right.

DR. GOLD: So, --

DR. HASEMAN: So, you're not comparing it to a paired control group. You're comparing -- the historical controls are themselves a low dose group of fluoride.

I mean, you could think of it that way.

DR. GOLD: And our lowest dose is zero incidence. That's -- that's where we're going from.

DR. GALLO: I'd like to call the question. I've got a motion and a second for no evidence of carcinogenic activity in the mice and rats.

It's been seconded, all in favor. Hands up, please.

(Hands are raised.)

1 for "No Evidence"

DR. GALLO: There is only one up.

Opposed?

(Hands are raised.)

DR. GALLO: Abstain?

Motion fails.

I would like to now turn to our primary reviewer for a motion.

DR. LONGNECKER: I'd like to move that the committee accept the report with the understanding that there will be editorial changes to include clarity and completeness in response to the written comments of the reviewers and the discussion at this meeting, and specifically that we agree with the inclusion -- conclusions that under the conditions of the two-year dose water study there

was equivocal evidence of carcinogenic activity of sodium fluoride in male F344/N rats based on the occurrence of a small number of osteosarcomas in dosed animals.

There was no evidence of carcinogenic activity in female F344/N rats receiving sodium fluoride at concentrations of twenty-five (25) one hundred or a hundred seventy-five parts per million (175 ppm), also given as parts per million of fluoride in the drinking water for two years.

There was no evidence of carcinogenic activity of sodium fluoride in male or female mice receivin sodium fluoride in concentrations of twenty-five, one hundred, or a hundred seventy-five parts per million (175 ppm) in drinking water for two years, that dosed rats had lesions typical of porosis in the teeth and high dose female rats had increased osteosclerosis of long bones.

And then we would like to make the suggestion that the statement that now appears on page ninety-three (93) be added to the conclusions, and that statement is: taken together the current findings are inconclusive but are weakly supportive of an association between sodium

fluoride administration and the occurrence of osteosarcoma in male rats.

DR. GALLO: Thank you.

Do I have a second?

(No response.)

DR. GALLO: Any discussion?

DR. ASHBY: Second.

DR. GALLO: Second by Doctor Ashby.

Any discussion?

Doctor Gold?

DR. GOLD: I'm more comfortable with putting into the conclusions -- the conclusion under male rats equivocal the definition that's used in the level of evidence --

DR. GALLO: (Interposing) That's implied by -- that's implied right in there.

When you say equivocal evidence, that's it.

And I would remind everyone, if I may, I'll do what Doctor Gold did before lunch, the definition of equivocal evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related, and I think that's what we have heard.

DR. GOLD; And it's called one category for uncertain findings in the definition.

DR. GALLO: That's it.

DR. ASHBY: That's it.

DR. GOLD: I like that word, "uncertain findings".

DR. GALLO: That -- that's --

DR. ASHBY: We left the word inconclusive in there, too, --

DR. GALLO: (Interposing) That's right.

DR. ASHBY: -- in this motion.

DR. GOLD: But you also have weakly supportive of an association.

It's equivocal, I guess, but I'm much more comfortable with "uncertain findings".

DR. DAVIS: I think the point is well taken to say they're uncertain, or equivocal, sort of implies you don't know one way or the other.

To say weakly supportive comes down on the side of, no matter how slight, to say that there is some positive effect.

And so I don't think they're the same.

DR. GALLO: Doctor Ashby?

DR. ASHBY: While I just seconded this motion,

there is a deeper issue under this, and that is what was discussed in my written comments whether on this occasion we can actually not use the normal classifications.

That's what we're beginning to talk about with those last comments, that we don't permit ourselves to the form of "equivocal evidence" or "some evidence", or "no evidence", but construct a phrase which describes the findings.

And I think it's rather dangerous myself. Although, I did propose it, I think we've got to stick with it, and the real duty is to inform the public, in general, what is meant by this term "equivocal" evidence, and if they rush off and misinterpret it, then ultimately that is their problem and not ours, as long as the information is there that actually transposes. I think we're adding to the confusion by making this different to the previous four hundred (400) reports.

DR. GALLO: The chair certainly agrees with that.

I mean, we may -- we may want to -- in adding that sentence that Doctor Longnecker mentioned, we may want to wordsmith that differently, but I don't

think we should touch the "equivocal".

That's my own opinion.

DR. GOLD: Pardon me. I'm not understanding.

DR. GALLO: In -- in the motion Doctor Longnecker suggested that we add the sentence "taken together the current findings are inconclusive but are weakly supportive of".

What you're saying is that that phrase, "are weakly supportive of" is of concern to you.

DR. GOLD: I would rather stick with the definition of equivocal --

DR. GALLO: (Interposing) Then, --

DR. GOLD: -- as it is on page four.

DR. GALLO: Then, I think we have to -- well, let me get a comment from --

DR. CARLSON: Yeah, I -- I agree with Doctor Longnecker's proposal for his motion.

If you don't put in "as weakly supportive" then the question is, well, then what do you mean?

If it's not supportive, -- if it wasn't supportive at least weakly, then I would have voted for the first motion.

DR. GOLD: For -- oh, but we've voted several re- -- several hundred reports with "equivocal".

DR. CARLSON: No, I have no -- I have no problem with "equivocal".

DR. ASHBY: See, the bit of a problem is, we discussed this yesterday, it says "may be associated", --

DR. GALLO: (Interposing) That's right.

DR. ASHBY: And what you really want to say and break the rules of grammar is "may" or "may not be" and that's the message you want to get across.

DR. GALLO: (Interposing) Well, that is the broken rule of grammar, isn't it?

DR. ASHBY: I know, that's what I just said.

DR. GALLO: That cost me a lot of knuckles.

DR. ASHBY: I said we need to understand what's under this. It's the "may not be" is emphasized, and people run away with the "may be", and this is why --

DR. GOLD: (Interposing) Perhaps we could use this very phrasing on page four which says that this is a category for uncertain findings. It's the definition here where --

DR. SILBERGELD: (Interposing) But that goes along with it.

DR. GALLO: That goes along -- I mean, what

you want to do is put it up front in the conclusion statement.

I don't have any problem with that as long as our --

DR. ASHBY: (Interposing) Just redefine the term, and yet --

DR. GALLO: Redefine the term, yes.

Doctor Garman?

DR. GARMAN: But I think "weakly supportive" in many people's mind is more than "equivocal". "Weakly supportive" means, yes, it's weak but it supports the idea that fluoride is related to thes tumors.

And what we're trying to say is we really don't know, and so I don't think that's -- I think that sentence is fine for the text, but I don't think it should be highlighted in a summary page that it is weakly supportive, because some people will take that as indicating that it is supportive somewhat, and therefore should be used in extrapolation to human population risks.

DR. GALLO: I mean, you could just -- you could truncate it and say taken together, the -- the current findings are inconclusive as to the

relationship between the administration and the osteosarcomas, you can truncate the sentence that way.

DR. GARMAN: That would be okay.

DR. GALLO: But I didn't -- that's not the motion on the the floor.

The motion would have to be amended or altered.

DR. ASHBY: I -- I was just saying that I'm on the verge of withdrawing my second actually, because if we are going to define the term up front in it text then I think that satisfies my concerns.

My concerns are people misinterpreting what equivocal means by not bothering to find this page six or whatever it is, and just rushing off

DR. GALLO: Fine.

DR. ASHBY: If it's defined in the frame, then I have to support it after you bring the extra phrasees in because deviations from normality are not usually used.

DR. GALLO: I support that.

Doctor Silbergeld?

It's back to Doctor Longnecker, now.

Doctor Longnecker, now, you want to rephrase

the motion?

DR. LONGNECKER: I would like to let all of the motions stand through the printed text which ends with increased osteosclerosis of long bones, and then I would like to let Doctor Gold propose an additional sentence.

DR. GALLO: Thank you.

DR. GOLD: Thank you, Doctor Longnecker.

DR. HART: So, this is an amendment?

DR. GALLO: No, no, the motion is going to be reworded.

Second was withdrawn.

(Discussion among Panel members.)

DR. GOLD: After the words "osteosarcomas in dosed animals" I move that we insert the sentence --

DR. SILBERGELD: Where are we?

DR. GOLD: We are at the end of the first sentence of the conclusion, "equivocal evidence is a category for uncertain findings, --

DR. GALLO: Fine.

DR. GOLD: -- period.

DR. GALLO: Do I have a second?

DR. ASHBY: I second it.

DR. HART: That -- excuse me, is that a parentheses or --

DR. GALLO: No, it's just another sentence.

DR. GOLD: No.

DR. HART: Another sentence.

DR. GALLO: Doctor Silbergeld?

DR. SILBERGELD: I'm also a little uncomfortable with tampering with things beyond the usual way in which we do business.

You know -- I have to say that in reading this document and preparing to come to this meeting, I spent a great deal of time trying to keep out of my mind that we were dealing with sodium fluoride, and trying to approach this document and the data here as if were some compound of unknown prevalence of exposure.

And I now see us kind of attempting to temper what we're saying in light of, that we know it's sodium fluoride, and bringing to bear concerns and facts that have nothing to do with the data in this document, frankly.

And some commentators have spoken to their concerns, that there are implications in the text that go beyond the charge to this study, and I

think we should be very careful to avoid those.

To that extent I think that if we're going to add material that explains what this particular category means, I would urge that we add all the material and not edit it out. I mean, that there are -- the definition of equivocal evidence is stated quite clearly on page four.

In my opinion, we don't need to state it again, but if we feel that we do, for nonscientific reasons, then I would urge we state the whole definition and not part of it.

DR. ASHBY: You could just extend the sentence, so that you could put in as a category --

DR. GALLO: (Interposing) That's right.

DR. ASHBY: And then define as follows, just put the words in.

I think I agree with that, too.

DR. GALLO: Doctor Carlson?

DR. CARLSON: Yeah, I was going to agree with Ellen because on certain findings, the findings are not uncertain, it's the relevance.

DR. GALLO: That's true.

I -- Lois, would you accept that?

DR. GOLD: I would be very happy to amend the

amendment.

DR. GALLO: So, it's equivocal with the whole definition of what equivocal is in the conclusion, is that my understanding?

DR. GOLD: As long as we include that it's the category for uncertain findings, as well.

DR. GALLO: Yes, that's correct.

DR. ASHBY: And probably just --

DR. HART: I accept the staff recomendations?

DR. GALLO: Yes. The motion --

DR. HART: (Interposing) So, are we including the definition of "equivocal evidence" and the "uncertain finding" thing?

DR. ASHBY: Yes.

DR. GALLO: Yes, that's correct.

DR. GOLD: Yes.

DR. HART: That first, or how? What order?

DR. GALLO: Now, we're going to -- if I understand the motion, we're going to accept the staff's recommendation with the definition of "equivocal" and "uncertain" at the end of it, is that correct?

DR. LONGNECKER: Yes.

DR. CARLSON: Again, I have to object. The findings aren't uncertain and so I -- I --

DR. GOLD: But, that's the definition --

DR. GALLO: No, that's within the definition.

DR. GOLD: That's within the definition.

DR. GALLO: Within the definition.

DR. CARLSON: What she had tagged on the end, we're not going to put it on the end anymore?

DR. ASHBY: It's using this phrase, equivocal is a category.

DR. GOLD: "Equivocal evidence is a category for uncertain findings defined as studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related."

DR. ASHBY: So, the marginal increase is accepted.

It's not that -- it's uncertain.

DR. GALLO: Okay.

Ready to vote?

DR. SILBERGELD: You know -- the more we do this, the more I would recommend we don't do this.

DR. GALLO: You guys -- it's your committee.

DR. SILBERGELD: Thank you, Doctor Gallo.

DR. GALLO: I'm just sitting here.

DR. SILBERGELD: I feel that a -- I know that a great deal of work has gone into what's on page four. A tremendous amount consideration of this language has gone on by our predecessors and by NTP.

And I think that it has borne the test of time, as being representing sound judgment, sound judgment principles, and as clear a statement of communication as can possibly be made.

By excerpting and rearranging, I think, we are -- you know -- lending ammunition, inadvertently or whatever to one side or another in this obviously extremely heightened subject.

I would like to state again, I would wish us just to leave the judgment alone as we would for any other chemical, might I remind you, the Panel, and refer people, if we want to put something in parentheses, I'd say for an explanation of terms, please see page four.

DR. GALLO: That's fine, too.

I mean, we've done that before.

That has been done before.

Doctor Ashby?

DR. ASHBY: Well, I -- I'm sensitive to what

you're saying, but on the other hand, I think if we are using a term there should be nothing wrong in defining it at the time, that's not pushing either way.

If we're using a term you can define it, and you should make sure people know what you mean.

And if that title must go further, because someone raised this point yesterday. This word "equivocal" is confusing, and it may well be worth putting it in all future reports so that people do know what it means.

So, I'm maintaining my second.

DR. GALLO: Jay?

DR. GOODMAN: I would ask that we vote on Doctor Longnecker's motion as amended by Doctor Gold.

DR. GALLO: I was going to take it one more time around.

All right. The motion on the table, as I understand is for the call on the recommendation of -- of the NTP that is equivocal, and the motion that has been seconded is that the definition of equivocal from page four be included in that motion.

DR. HART: The hybrid -- the hybrid definition --

DR. GALLO: It's hybrid definition, that's correct.

It's not --

DR. GOLD: Would you like to read how it is?

DR. CARLSON: We're not going to vote on the amendment separately, because it's really not -- it's really a part of the original --

DR. GALLO: (Interposing) Well, I think maybe that's an approach. That's a good idea.

DR. SILBERGELD: Why don't we do that?

DR. GALLO: If the -- Doctor Longnecker would -- would allow us to split that out without the amendment, I would like to get that out of the way.

Is that --

DR.. DAVIS: I thought it wasn't an amendment. I thought he allowed her to finish his motion.

It was not really a amendment.

DR. ASHBY: And I seconded that.

DR. GALLO: All right. Then we can -- then, we're voting only on the equivocal.

DR. ASHBY: No, we're not.

We're voting on the classification

"equivocal", plus this definition which is a phrase, uncertain findings defined as follows.

DR. GALLO: All right. Let's vote it and see what happens. Let's go that way.

I don't have any big problem with that.

All in favor of the motion as stated and amended?

(Hands raised.)

DR. GALLO: Opposed?

(Two hands raised.)

DR. HART: Nine to two.

DR. GALLO: Abstained?

(No response.)

DR. GALLO: None.

Okay. Yes, sir?

DR. ASHBY: I think it's worth specifically putting in the minutes that the -- that the contrary votes were because of the amendment not because of a controversy of evidence..

DR. ZEISE: That's correct.

DR. GALLO: I would like to -- I would like to have a --

DR. DAVIS: Let's draw atten- -- it is not an amendment.

DR. GALLO: That's correct. It is not an amendment.

DR. DAVIS: There is no amendment.

DR. GALLO: That's correct. It is not an amendment. It's part of the motion.

DR. DAVIS: What we have here is a motion that he made the first part and she filled out to make the second part. There was no --

DR. ASHBY: But the negative votes were having the word defined in front and --

DR. GALLO: Yes, and I would like to have that in the minutes.

DR. DAVIS: But not an amendment.

DR. GALLO: That there was no question of the equivocal call.

All right.

DR. ZEISE: Now, I think it's possible that had we split it we would have gotten a different vote.

DR. GALLO: That's why I tried to avoid that.

DR. SILBERGELD: That's right

DR. GALLO: That's fine.

I think we're all right.

I mean, we may have, and --

DR. ZEISE: (Interposing) Well, I think I can count --

DR. GALLO: (Interposing) Oh, I can, too.

I think you have -- we have a -- I think that the minutes should show that we have, and that's why I wanted to split it. I mean, basically we have unanimity on the equivocal and it's a question of the wording.

Okay.

DR. ALLABEN: Mr. Chairman, may I ask for a reading as stated?

Larry, would you reread what the motion was and voted on, please?

DR. HART: Okay. Doctor Longnecker made the motion --

DR. GALLO: You need a microphone.

DR. HART: Okay. Doctor Longnecker moved that -- that the report be accepted with the revisions as discussed and the conclusions accepted as written.

And then he reads -- read the conclusions that are on page three. I don't think I need to read all that.

DR. DAVIS: Page two.

DR. HART: Down through the sentence that reads "Dosed rats had lesions typical of fluorosis of the teeth and in high-dose female rats had increased osteosclerosis of long bones."

I'm not quite sure how the wording goes here, but with the separate statement following this that, "equivocal evidence is a category for uncertain findings that is demonstrated by studies that are interpreted as showing a marginal increase in neoplasms that may be -- may be chemically related".

Everybody agree with that?

DR. ALLABEN: Then there was nothing else that was added?

DR. HART: No.

DR. GOLD: I had intended to put it after the first sentence, but I don't really care where you put it.

DR. GALLO: Why don't we leave it there?

DR. HART: Okay. Yeah, I believe you're right on that. That's what it relates to.

DR. GALLO: Everybody comfortable?

No, not comfortable?

Would you like to make another motion before we go home?

DR. ZEISE: I don't know if we can revisit this again, but I would like to get a reading on how many would have voted otherwise had the wording been left out.

DR. GALLO: I think under Roberts Rules of Order, I can actually entertain a motion to do that.

DR. ZEISE: You can?

DR. ASHBY: That's not the motion you wanted, that we voted on equivocal evidence.

DR. GALLO: That's what I would like to --

DR. ASHBY: Just say it's going to be unanimous.

DR. GALLO: Yes. I would like --

DR. ASHBY: (Interposing) It still doesn't replace the other motion. It's just a majority, but at least it will show you where the differences lay, so I proposed then that we -- that we agree that there is equivocal evidence in the male rats of osteosarcomas.

DR. GALLO: Second?

DR. GOLD: Second.

DR. GALLO: In favor?

(Hands raised.)

DR. GALLO: Now, we got it.

Opposed? All right.

Thank you.

DR. HART: Whoah! Wait a minute, we're still counting.

DR. GALLO: You have got an opposed?

DR. HART: Yes.

DR. GALLO: Oh, I'm sorry.

Two opposed.

DR. DAVIS: No, no, no. I was for the motion. I thought you were going to recount again. You stood up like he was about to count.

(Laughter.)

DR. GOLD: You voted for equivocal evidence.

DR. GALLO: The motion was for clarification, that without the -- the other sentence, that there is equivocal evidence for carcinogenic activity in the male rats as stated in the report. It was seconded and that's what we were voting on.

And Doctor Davis was making sure we got his count, I believe?

DR. DAVIS: Right.

DR. GALLO: So, all in favor or the motion for equivocal evidence in the rat, as stated.

(Hands raised.)

DR. GALLO: That's it. Fine.

Thank you.

Opposed?

(No response.)

DR. GALLO: None.

Okay. I want to thank everybody.

This has been a tough two days. It's been a lot of hard work, and I think you all deserve a lot of support for what you've done.

Thank you very much.

DR. GRIESEMER: Thank you all from -- from NIEHS, NTP.

---

(WHEREUPON, THE MEETING WAS ADJOURNED AT 2:23 P. M.)

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4-26-90:MPC:wbb:5-9-90

*SCIENCE*

# Don't Drink the Water?

## Brush your teeth, but the fluoride from your tap may not do much good—and may cause cancer

Remember the great fluoride debate? Back in the 1950s, every voice of authority, from the U.S. Public Health Service to the PTA, supported adding fluoride to the water supply as an effective and totally safe way to promote healthy teeth. The only opponents seemed to be John Birchers and other extremists who regarded the scheme as a diabolical communist plot. In the years since, most of the nation's major cities fluoridated their water, and the issue appeared closed. No less an objective voice than Consumer Reports declared in 1978, "The survival of this fake controversy . . . epresents one of the major triumphs of quackery over science in our generation."

In fact, the debate never ended. Now it may explode as never before, posing new challenges to medical dogma and giving parents one more thing to worry about. Government researchers have new evidence that casts doubt on the benefits of fluoridation and suggests that it is not without risk. The most incendiary results come from the National Toxicology Program (NTP), which in 1977 was ordered by Congress to determine whether fluoride causes cancer. This week NTP plans to release data showing that lab rats given fluoridated water had a higher rate of a rare bone cancer called osteosarcoma. According to a memo by the Environmental Protection Agency, "very preliminary data from recent health studies . . . indicate that fluoride may be a carcinogen."

Fluoridation proponents are already criticizing the NTP study, but it will be harder to discredit or ignore than the hundreds of earlier experiments, of varying quality and from around the world, that have linked fluoride to mottled teeth, skeletal damage, genetic defects and other ills. During the two-year experiment, rats and mice drank water with different levels of sodium fluoride. None of the animals drinking fluoride-free water developed cancer, nor did any of those drinking water with the lowest fluoride concentration, 11 parts per million (ppm). But of the 50 male rats consuming 45-ppm water, one developed osteosarcoma. Four of 80 male rats drinking 79-ppm fluoride developed osteosarcoma. No mice or female rats showed signs of bone cancer. Although the animals drank higher concentrations of fluoride than people do (the legal standard is four ppm), such megadosing is standard toxicological practice. It's the only way to detect an effect without using an impossibly large number of test animals to stand in for the humans exposed to the substance.

Although the final NTP report will not be released for months, several independent toxicologists find the results significant. Most important, the rats who did not drink fluoride did not get cancer, indicating that the malignancies are "not a fluke," says EPA scientist William Marcus. There is also a convincing relationship between dose and response: the more fluoride, the more cancers. Pathologist David Kaufman of the University of North Carolina warns that the rat data must be examined to see if the cancers appeared in the long bones of the arms and legs, as osteosarcomas do in humans, or in other places, which might make the results less relevant to people. Still, Kaufman says the NTP data "make fluoride look like a weak carcinogen. It's obviously something to worry about"—but not panic over. There are about 750 cases of osteosarcoma in the United States annually; even if fluoride caused all of them—an impossibility—the lifetime risk to any individual from drinking fluoridated tap water would still be only about one in 5,000.

**Too crude:** If fluoride causes bone cancer in lab rats, then why, after 45 years of fluoridation, haven't researchers seen a rash of osteosarcomas in fluoridated cities? Because epidemiology is too crude to detect it even if the cancers are there. In the 1970s, the National Cancer Institute found no sign of higher cancer rates in fluoridated

**From the beginning, controversy:** *In 1965, the protests reached the reservoir's edge*

UPI-BETTMANN NEWSPHOTOS

ROB NELSON—BLACK STAR

**Fluoridation:** *Atlanta's waterworks*

## Fluoride Facts

- Fluoride—in water or toothpaste—helps teeth resist decay. It seems to work by redepositing calcium and other ions in tooth enamel, repairing and strengthening it.
- 53% of the U.S. population drinks water containing fluoride. 121 million people have artificially fluoridated water; 9 million drink from naturally fluoridated supplies.
- 41 of the 50 largest U.S. cities have fluoride in the water; those that don't include L.A. and San Diego.
- The legal standard for fluoride in drinking water is four parts per million; for toothpastes, 1,100 ppm.

cities. But that reassuring finding may be misleading. According to Donald Taves, a fluoride expert, if the difference were anything less than 7 percent it would not be detectable. Another obstacle to definitive epidemiology is mobility: just because someone got osteosarcoma in a fluoridated city does not mean he had been living there all his life.

The NTP results assume an added importance when combined with recent data on the shrinking benefits of fluoridation. According to the American Dental Association (ADA), tooth decay is anywhere from 50 to 70 percent less in fluoridated areas. But figures from the National Institute of Dental Research (NIDR), part of the National Institutes of Health, suggest otherwise. A 1987 survey of almost 40,000 schoolchildren found that tooth decay had declined sharply everywhere. Children who had always lived in fluoridated areas had 18 percent less decay, compared with their peers who had lived in nonfluoridated areas. This 18 percent translates into a difference of fewer than one cavity per child. Similarly, in a 1986 paper in the British journal Nature, Australian researcher Mark Diesendorf assessed 24 studies from eight countries and found that cavity rates had declined equally in fluoridated and nonfluoridated areas, suggesting fluoridated water isn't that important.

How can that be? "A good ...e can be made that it has to ...o with fluoride in toothpaste and rinses," says dental-health expert Brian Burt of the University of Michigan. And even if drinking fluoridated water is slightly risky, there is no hint that fluoridated toothpaste—as long as you don't swallow any—is dangerous. Tooth decay may also be declining because of better diet and hygiene. Also, foods and beverages processed with fluoridated water are ubiquitous. (Many bottled waters, though, do not have fluoride.) As a result, argues Alan Gray, a leading pro-fluoridation dentist in Canada, "it is becoming difficult to provide accurate, ethical advice" about fluoridation.

Among environmental controversies, fluoridation is unique in that one side has consistently denied that questions of risk or benefit even exist. The ADA states, "Anti-fluoridation groups attempt to create the illusion of a scientific controversy [which is] merely a ploy to create doubt about a well-researched, well-demonstrated preventive measure." But even well-researched articles raise hackles. When, in 1988, Chemical & Engineering News presented a balanced report on fluoridation, it attracted the wrath of the medical establishment. Says Taves, "Too many scientists lost their objectivity. This has become a religion on both sides."

**Safe water:** And that undercut the scientific process. The NIDR kept files on people perceived as threats to fluoridation. Political decisions were at odds with expert advice: a panel convened by the surgeon general in 1983 expressed concern, in closed sessions, about skeletal and dental damage from fluoride. At one point, a member said, "You would have to have rocks in your head, in my opinion, to allow your child much more than two parts per million [fluoride]." Said another, "I think we all agree on that." Even so, in 1986 EPA *raised* the fluoride standard from about two ppm to four.

This month EPA opened a review of the standard. Once EPA receives the official NTP report, it will establish a target "safe" fluoride level. The Safe Drinking Water Act requires that the level be zero for carcinogens, but the standard may be based on what is technically feasible. Fluoridation can be stopped immediately, but many communities with naturally fluoridated water—up to 12 ppm—would have to remove it. As EPA wrestles with the standard, fears John Sullivan of the American Water Works Association, "confusion will reign": local laws will still require fluoridation, a practice that may cause cancer.

As they await EPA's decision, pro-fluoridationists are invoking arguments of social justice. Dental researcher Ernest Newbrun of the University of California, San Francisco, contends that fluoridation promotes the health of children of "all races and all socioeconomic classes," not only those with enough money or discipline or access to the health system to take a fluoride supplement every day. He and others say it is morally wrong not to provide the benefits of fluoride. Although the NIDR's and other surveys suggest that fluoride in toothpastes and dental rinses also ensures healthy teeth for those who use the products, those who do not might suffer.

No one can foresee how the fluoride debate will play out this time. But since the 1950s, the country's environmental consciousness has been heightened. In the end, deciding whether or not to fluoridate turns less on science than on values. The sheer weight of good research may finally, after four decades, begin to inform those judgments and even overwhelm the unscientific rhetoric that has characterized both sides of the debate for far too long.

SHARON BEGLEY


PHOTOS BY JACQUES CHENET—NEWSWEEK

**After every meal:** *Toothpastes to fight cavities*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27709

March 12, 1984

The Honorable Norman F. Lent
House of Representatives
Washington, D.C. 20515

Dear Mr. Lent:

Your letters to the National Cancer Institute (NCI) and the Food and Drug Administration on behalf of Ms. Eleanor Krinsky, Plainview, New York, regarding our testing efforts on sodium fluoride have been forwarded to me for reply. A background and status of our studies on this important chemical follows:

In 1977 the Congressional Subcommittee on Intergovernmental Relations and Human Resources requested that the National Cancer Institute determine if fluoride had any carcinogenic potential in experimental animals. In response the NCI and the National Toxicology Program (NTP) implemented studies at Battelle Columbus Laboratories in late 1979 to determine the potential for sodium fluoride (NaF) to cause cancer and/or other toxicities in rodents.

In most cases the assessment of the carcinogenic potential and the toxicity of a chemical is undertaken in several phases. Initially, subchronic studies of various durations (usually 14 and 90 days) are performed and the results are used to evaluate the cumulative effects of repeated administration and to assist in determining doses of the chemical which can be administered to rats and mice throughout a two-year chronic study. The second phase is the chronic study: after exposing the rats and mice to the chemical for two years the collected data are analyzed, and an evaluation is made concerning the toxicology and carcinogenicity of the chemical. Following peer review by the NTP Board of Scientific Counselors, this information is disseminated in the form of a detailed Technical Report, the availability of which is announced in the Federal Register. Regarding these studies on sodium fluoride, the NTP anticipates a delay in the issuance of the Technical Report on NaF due to the necessity to repeat the chronic study. The reason for this delay and the measures the NTP will take to minimize the inconvenience caused by this delay are outlined below.

The testing of NaF in animals is divided into three parts. The first subchronic study consisted of exposing rats and mice of both sexes to concentrations of NaF in drinking water ranging from 0 to 800 ppm for one month. Animal mortality was monitored during the study and these data were used to select doses for a second subchronic study. The second study employed doses of 0-300 ppm (rats) and 0-600 ppm (mice), and lasted six months. At the conclusion of the second study data were collected on

animal mortality, weight gain, clinical signs, and gross and histopathologic changes. This information was used to estimate the maximum doses of NaF which rats and mice could be expected to tolerate throughout a two-year study without adversely affecting longevity.

The two-year studies were begun in December 1981 using groups of 60 rats and 80 mice/sex/dose exposed to doses of 0, 10, 30, and 100 ppm NaF in drinking water. After the first year of exposure 10 mice and 10 rats/sex/dose were killed and examined for gross and histopathologic changes, and the sera from these animals were analyzed for alkaline phosphatase activity, and for fluoride, calcium, phosphorous, zinc and manganese content. In addition, bone fluoride and calcium content and liver zinc and manganese concentrations were determined. These chronic studies were terminated on schedule in December 1983. Gross necropsy examinations were done on all animals, including those which had died prior to the end of the study. Complete histopathologic examinations are currently being done on ten randomly selected animals/sex/species which had survived to termination from the control (0 ppm) and high dose (100 ppm) groups. Similar elemental and enzyme analyses of sera and bone as were performed at the one-year scheduled kill will be performed on samples collected during the termination of the study.

Unfortunately, after about seven months into the NaF chronic study problems were encountered. While no overt clinical signs were observed in the mice, certain rats in both the NaF control and dosed groups showed signs of torticollis and ocular lesions. Even though this was clearly not a treatment related effect, a considerable amount of effort was expended in attempting to determine the etiology of these lesions. The presence of viral and mycoplasmic infections was ruled out, and a hereditary basis was considered, but appeared unlikely. Similar clinical signs to those observed in the rats in this study have been demonstrated to occur in animals raised on diets deficient in trace elements; therefore attention was directed to the diet used in the NaF study.

The diet employed in most NTP studies is the NIH-07 open formula diet. This diet was not used in the NaF study because fluoride is a common contaminant in the NIH-07 feed and the fluoride concentration can vary from batch to batch. Because we certainly wanted to limit exposure of the exposed animals to fluoride through the diet, a semisynthetic diet was adapted for use which could be formulated to contain fluoride at less than 3 ppm. While this diet had been shown adequate to sustain rodents, an analysis of the actual diet used in the chronic study revealed less than the recommended levels of manganese, chromium, choline, and vitamins D, $B_{12}$, and E.

At this time we cannot state with certainty that these apparent dietary deficiencies were the cause of the observed clinical signs in the rats. Nonetheless, the problems with the diet were considered serious enough to question the validity of the study as an adequate appraisal of the toxicology and carcinogenicity of NaF. For this reason a second chronic study using an adequate diet has been scheduled, and we anticipate that the

new chronic studies will begin in September or October 1984, exposure will be completed in October 1986, and that the Technical Report will likely be issued in early 1988.

Recognizing that this could prove to be disconcerting to individuals and groups which had anticipated the release of the results of the NTP study of NaF, the NTP will make available all data collected during the two subchronic and first chronic studies. These data are being compiled. Meanwhile, requests for more detailed information concerning the design and types of data collected in these studies and when these data may be obtained should be directed to Dr. John R. Bucher, Chemical Manager for the Fluoride Studies, National Toxicology Program, P. O. Box 12233, Research Triangle Park, NC 27709, telephone (919) 541-4532 or (FTS) 629-4532.

If I may be of further assistance, please do not hesitate to contact me.

Sincerely yours,

David P. Rall, M.D., Ph.D.
Director
National Toxicology Program

COMMONWEALTH OF PENNSYLVANIA

SUPREME COURT
SIX GATEWAY CENTER
PITTSBURGH, PENNSYLVANIA 15222

JOHN P. FLAHERTY
JUSTICE

October 30, 1981

Mr. Brian Turvey
BBC-TV
Broadcasting House
Llandaff Cardiff
Wales, United Kingdom

Dear Mr. Turvey:

Please excuse my delay in responding to your inquiry and request, as I have been in Philadelphia for approximately two weeks, and have just returned to my Pittsburgh complex.

Some few years ago, while I was a Judge of the Court of Common Pleas, I presided over a protracted trial involving the introduction of sodium fluoride into the public water supply at the rate of one part per million. The case required six weeks of trial time and called into my court the luminaries of the scientific community on both sides of this perplexing issue. My recollection is that the transcript consists of 2800 pages of complex testimony. My Opinion and Order is enclosed herewith. Since that time, the case has been languishing in the Commonwealth Court of Pennsylvania, an intermediate appellate court, on the question of jurisdiction, i.e. whether the question is exclusively in the Department of Environmental Resources, or, at least concurrently within the jurisdiction of a court of equity.

The findings of fact are not an issue at the present time.

Since my decision, I have received voluminous correspondence from all parts of the world on this subject. I enclose a representative sample. Recently, I have received information that the Province of Quebec has suspended the practice of fluoridation, and I am advised that scientific inquiry has been exacerbated as of recent date. Particularly, I call your attention to the enclosed article which appeared in the Journal of the American Chemical Society authored by Emsley et al., contributed by Kings College, the University of London, and Brock University of Ontario, Canada.

It is my reflective judgment that fluoridation of the public water supply could well be a practice which produces extraordinary deleterious effects to the human system which disrupts and destroys important biostems over a long span of time, and it is obvious that the far-reaching consequences of this have not been fully examined yet or even admitted by the advocates of the practice. It is with a great deal of trepidation that I look fearfully upward as a great hand moves over us--and it is not the hand of God--but of science, emotionless, remote, objective to the point of monstrosity! I shudder at our stupidity. My somewhat inadequate opinion well-speaks to this point, and I need make no comment.

I hope this answers your inquiry.

Very truly yours,

JOHN P. FLAHERTY
Justice
Supreme Court of Pennsylvania

JPF:pld

Enclosures

The United States National Academy of Sciences has set forth the following guidelines regarding the use of animal testing to determine the cancer-causing ability of chemicals in humans.

1. ". . . cancer induction in experimental animals, even with the most potent carcinogenic chemicals, requires at least several months and in many instances a whole lifetime."[1]

2. "On a body weight basis, man is generally more vulnerable than the experimental animal, probably by a factor of 6-12."[2]

3. "Effects in animals, properly qualified, are applicable to man."[3]

4. "Methods do not now exist to establish a threshold for long-term effects of toxic agents [i.e. if a substance is shown to cause cancer at a particular dose, 1/10th of the dose will cause 1/10th of the number of cancers, 1/100th of the dose will cause 1/100th of the number of cancers, etc.]"[4]

5. "The exposure of experimental animals to toxic agents in high doses is a necessary and valid method of discovering possible carcinogenic hazards in man. . . . To obtain statistically valid results from . . . small groups of animals [relative to the size of the human population at risk] requires the use of relatively large doses so that effects will occur frequently enough to be detected."[5]

6. "The actual risk to humans might be even greater over a human lifetime, because it is 35 times that of the mouse".[6]

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[1] Drinking Water and Health (National Academy of Sciences, Washington, DC, 1977) p.52
[2] ibid, p.52-53
[3] ibid, p.53
[4] ibid, p.54
[5] ibid, p.55
[6] ibid, p.55

January 22, 1990

**National Toxicology Program (NTP) Study of Chronic Toxicity and Carcinogenicity of Sodium Fluoride – FACT SHEET**

NTP Study:

Sodium fluoride was administered in the drinking water at concentrations of 0, 25, 100, and 175 ppm (equals 0, 11, 45, and 79 ppm fluoride) to groups of male and female F344 rats and B6C3F1 mice, for two (2) years. There were 80 animals in the control and high dose groups, and 50 in the low and mid dose groups.

The study is now in the evaluation phase. A panel of pathology experts evaluated the histopathology diagnoses on January 12. This review group has confirmed the preliminary findings of osteosarcomas in male rats (incidences of 0/80 in control rats, 0/50 in the low dose group, 1/50 in the mid dose group, and 4/80 in the high dose group) and squamous carcinomas in the tissues of the oral cavity in male and female rats (Male: 0/80 control, 0/50 low dose, 1/50 mid dose, and 1/80 high dose; Female: 1/80 control, 0/50 low dose, 0/50 mid dose, and 3/80 high dose). Both rats and mice had dose-related fibrosis of bone and female rats had osteosclerosis of long bones.

Validated (but as yet uninterpreted) pathology data tables will be available on Mon or Tues approximately February 2. The entire data set along with statistical analyses, comparisons with historical control tumor incidence data and an interpretation of any potential biologically significant findings will be available in a draft Technical Report in mid-March. This report will undergo comprehensive peer review in an open-to-the-public meeting by the NTP Board of Scientific Counselors in mid-April.

Call Nim Brown (HHS) on monday to get on list for tables | 245-6867 Then he will know when tables will be ready

Dr. Jonn R. Bucher
NIEHS
P.O. Box 12233
Research Triangle Park, NC 27709

Dear Dr. Bucher,

This is a request under the Freedom of Information Act for

(1) all information that you or the NIEHS have including methods, results, conclusions, discussion, or any other communications (oral, written, or any other) regarding carcinogenicity studies done by Proctor and Gamble since 1983. In particular, I should like to have any and all information that you have with regard to an unpublished study done by them about 2-3 years ago, which was mentioned by you in a discussion with Dr. Robert Carton of the Environmental Protection Agency.

(2) all information that you or the NIEHS have including methods, results, conclusions, discussion, or any other communications (oral, written, or any other) regarding the National Toxicology Program's studies on sodium fluoride. In particular, I should like to have any and all information that you have with regard to the results of the microscopic evaluations before they were sent to the peer review panel.

In fulfilling this request, you may exclude social security numbers and individual salary information and names of and identifying details about staff who are not listed as key personnel.

Sincerely,

John Yiamouyiannis, Ph.D.
6439 Taggart Road
Delaware, Ohio 43015

9/18/89

cc: James Turner, Esq.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 2770

March 27, 1989

Paul S. Beeber, Esq.
New York State Coalition
Opposed to Fluoridation, Inc.
P.O. Box 263
Old Bethpage, New York 11804-0263

Dear Mr. Beeber:

Regarding your letter of March 8, 1989, concerning the National Toxicology Program (NTP) studies of sodium fluoride, I can report to you that the contract laboratory that performed the animal studies has completed their initial evaluation of the tissues, and has submitted draft reports to us. We are awaiting submission of the residual tissues and microscopic slides to the NTP so we can begin our review of the study materials. There are no results which we can currently release from this study. If our review proceeds as hoped, we should have pathology tumor incidence tables which can be made available by early next year.

We appreciate your continued interest in our studies.

Sincerely,

John R. Bucher, Ph.D.
Carcinogenesis and Toxicologic
Evaluation Branch

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Toxicology Program
P.O. Box 12233
Research Triangle Park, NC 27

February 6, 1990

Enclosed are the verified, but as yet uninterpreted, pathology data for the National Toxicology Program (NTP) study of the toxicity of sodium fluoride.

The National Toxicology Program conducted studies in two species of rodents to evaluate the long-term toxicity and carcinogenicity of sodium fluoride. As indicated in the tables, sodium fluoride was administered in the drinking water at concentrations of 0, 25, 100, or 175 ppm (equivalent to 0, 11, 45, and 79 ppm fluoride) to Fischer 344 rats and B6C3F1 mice (six weeks old at the start of the study) of each sex for two years.

There were 80 animals in each of the control and top dose groups and 50 in the low and mid dose groups. Ten additional animals per sex, species and dose were killed at 26 and 65 weeks; additional control animals were sacrificed in those weeks in which an animal in a dosed group died. The animals received a gross necropsy and histopathologic evaluation.

These pathology data, along with other information regarding the design, conduct, and interpretation of the NTP study on the long-term toxicity of sodium fluoride, will be assembled into a draft NTP report by staff members.

It must be emphasized that the scientific interpretation of these data is a complex process involving a number of scientific disciplines. Proper interpretation requires an understanding of the historical information concerning the variability of tumors and other lesions that occur normally in aged rodents of these strains and an appreciation of the most appropriate selection of study groups for statistical comparisons. Further, a very large number of statistical tests have been performed because of the large number of different cancer types and sites examined by the pathologists. Therefore, it is expected that a number of statistically positive results will be found in the data by chance alone. These issues clearly indicate that until the scientific evaluation is completed in April, interpretation of these data is premature.

It should also be emphasized that any determination of risk to humans from chemicals evaluated in animal studies requires a wider analysis that extends beyond the purview of these studies.

The report, available by April, will be peer-reviewed by the NTP Board of Scientific Counselors in an open-to-the-public meeting on Thursday, April 26, 1990.

Enclosures (18)

Note:
In 1978, Justice Flaherty made a landmark decision in a major court trial with lengthy he ngs and almost 3,000 pgs. of estimony, that he was "compellingly convinced" of the serious health hazards of fluoridation. His scientific background makes his decision even more significant.

COMMONWEALTH OF PENNSYLVANIA

SUPREME COURT
SIX GATEWAY CENTER
PITTSBURGH, PENNSYLVANIA 15222

Note:
In 1988, Justice Flaherty re-affirms his convictions that fluoridation is a very dangerous practice.
In correspondence he has written: "there is strong, indisputable evidence that fluoridation, even at 1 p.p.m., is extremely deleterious to the human system."

JOHN P. FLAHERTY
JUSTICE

January 26, 1988

Ms. Evelyn Hannan
Post Office Box 263
Old Beth Page
New York, New York 11804-0263

Dear Ms. Hannan,

Upon my return from Philadelphia I found your letter of January 19, 1988 and its enclosures dealing with the subject of fluoridation of the public water supply. Please excuse my delay in responding.

It has been years now since the case involving fluoridation was before me as a trial judge, but since that time nothing I have seen changes my view of the serious hazards occasioned by public fluoridation. To the contrary, what I have read convinces me all the more that indepth, serious, scientific effort should be undertaken before further expanding a questionable practice. Those who belittle critics of fluoridation do the public a misservice, yet it seems in the face of strong, uncontradicted prima facie evidence, that is the tactic most often employed.

Whether government has the right to force what it perceives as a benefit to the public was not directly before me in the case, but that also is to be pondered.

My hope is that groups such as yours* will spur the scientific community into an objective posture on this issue.

I enclose an essay which was sent to me a few years ago focusing on the issue presented by analyzing epidemiological law data. Perhaps resolution of this narrow question will provide the answer.

Thank you for writing.

Very truly yours,

JOHN P. FLAHERTY
JUSTICE
SUPREME COURT OF PENNSYLVANIA

* (Letter to New York State Coalition Opposed to Fluoridation, Inc.)

JPF/dct

(OVER)

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Dear Ms. Hannan,

Upon my return from Philadelphia I found your letter of January 19, 1988 and its enclosures dealing with the subject of fluoridation of the public water supply. Please excuse my delay in responding.

It has been years now since the case involving fluoridation was before me as a trial judge, but since that time nothing I have seen changes my view of the serious hazards occasioned by public fluoridation. To the contrary, what I have read convinces me all the more that indepth, serious, scientific effort should be undertaken before further expanding a questionable practice. Those who belittle critics of fluoridation do the public a misservice, yet it seems in the face of strong, uncontradicted prima facie evidence, that is the tactic most often employed.

Whether government has the right to force what it perceives as a benefit to the public was not directly before me in the case, but that also is to be pondered.

My hope is that groups such as yours* will spur the scientific community into an objective posture on this issue.

I enclose an essay which was sent to me a few years ago focusing on the issue presented by analyzing epidemiological law data. Perhaps resolution of this narrow question will provide the answer.

Thank you for writing.

Very truly yours,

JOHN P. FLAHERTY
JUSTICE
SUPREME COURT OF PENNSYLVANIA

(OVER)

* (Letter to New York State Coalition Opposed to Fluoridation, Inc.)

JPF/dct

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 277

Statement to Accompany Preliminary Data Tables from the NTP Two-Year Sodium Fluoride Study Performed Dec. 1981 to Dec. 1983- Prepared July 29, 1985

Due to the inadvertent use during the two-year drinking water study of sodium fluoride, of a low fluoride semisynthetic diet deficient in several vitamins and minerals, the National Toxicology Program (NTP) has declared the study inadequate for assessment of carcinogenic potential. No Technical Report will be issued on these data, and the NTP will not issue a formal statement of interpretation or summation of the study. However, the NTP is making the data available to the public. A second two-year study with sodium fluoride is scheduled to begin in October of 1985.

The data, in the form of summaries of individual animal pathology tables, are divided into compilations of neoplastic and non-neoplastic lesions. Additional tables contain statistical analyses of tumor incidence data. Incidences are given for male and female rats in the following dose groups: vehicle control, animals maintained on a low fluoride semisyntheic diet, and given distilled water; low dose, animals on the low fluoride diet given drinking water with 10 ppm NaF; mid dose, animals fed the low fluoride diet and given drinking water containing 30 ppm NaF; high dose, animals fed the low fluoride diet and given drinking water containing 100 ppm NaF. Groups of male and female mice received the same diet and fluoride dosed water as the rats, but an additional group of male mice served as a diet control, and are designated control(untr). These animals were fed NIH-07 diet, which is the customary open formula diet used by the NTP in two-year studies, and were given distilled water to drink. The tumor incidence analysis table for mice marked part 2 of 2 contains comparisons of tumor incidences between the dosed mice maintained on the low F semisynthetic diet, and the NIH-07 diet controls.

Specific questions concerning these tables should be directed to the Chemical Manager for the Fluoride studies, Dr. John R. Bucher, (919) 541-4532, or P.O. Box 12233, Research Triangle Park, N.C. 27709. Two initial points of clarification may be of assistance. There was little evidence of the development of fluorosis in either sex of rats or mice in this study. The diagnosis of deformity of the sternum in female mice was dose related, but consisted only of curvature of the sternum, noted on gross examination. No evidence of any abnormality was noted on microscopic examination, and the pathologist did not consider this "lesion" related to fluoride treatment, or to fluorosis. In addition, incidences of hepatocellular adenomas and carcinomas appear increased in dosed male mice when compared to NIH-07 diet controls (page 5, part 2 of 2, Intercurrent Mortality Adjusted Tumor Incidence Analysis for Mice), however, a comparison with the incidence observed in the control male mice given the low fluoride diet (page 6, part 1 of 2, Intercurrent Mortality Adjusted Tumor Incidence Analysis for Mice) does not show a significant dose effect, and suggests that hepatocellular tumor incidences in male mice were affected by the semisynthetic, low fluoride diet.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 2770

October 23, 1986

Phyllis J. Nostrant
55 West Genesee St.
Baldwinsville, N.Y. 13027

Dear Mrs. Nostrant:

Thank you for your interest in the NTP sodium fluoride studies. In reply to your request I have enclosed a copy of a previous status report which gives general information concerning the study designs and the problems encountered during our first 2-year toxicity and carcinogenicity study. To update this statement, our second 2-year study is currently underway. The design is similar to that of the first study except the doses used are 0 ppm, 25 ppm, 100 ppm, and 175 ppm sodium fluoride in drinking water. The diet being used is our standard NIH-07 diet and we are using batches of diet selected for low fluoride content (< 10 ppm). There are no data available from this second 2-year study as of yet. Although the first study was declared inadequate for assessment of carcinogenicity, and no formal data summaries have been prepared, raw data tables of neoplastic and nonneoplastic lesions are available, and I would be happy to forward copies of these if you are interested. The studies currently underway are proceeding very well and we anticipate no problems that will affect the interpretation of these studies.

Sincerely,

John R. Bucher, Ph.D.
Carcinogenesis and Toxicology
Evaluation Branch, National
Toxicology Program

Enclosure (1)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 27709

July 31, 1984

Dr. John Yiamouyiannis
Director, Center for Health Action
P.O. Box 1004
Delaware, OH 43015

In response to your June 27 request for data from the National Toxicology Program's sodium fluoride study I have enclosed a copy of the protocols and results of a one month repeated dose study, a 26 week prechronic toxicity test, and preliminary results from a two year chronic toxicity and carcinogenicity test. We have been informed by Battelle Columbus Laboratories that the initial pathology report on the animals killed at the conclusion of the two year study will be completed in April or May of 1985. Therefore, preliminary information will be available at that time, but the data will not be considered final until they are reviewed and approved by NTP pathologists.

As noted in the enclosed report, after a review of the clinical signs shown by the control and treated rats during the first two year study, scientists within the Toxicology Research and Testing Program (TRTP) had the semisynthetic low fluoride diet analyzed for essential nutrients. Deficiencies of several vitamins and minerals were discovered, and for this reason TRTP scientists declared the two year study inadequate for assessment of the potential carcinogenicity of sodium fluoride. In that this determination was made during the second year of the study, the test was allowed to continue to completion in the hope that the toxicity results would verify that maximally tolerated doses had been used, and could be used again in the anticipated repeat study.

TRTP is the division of the NTP which designs and administers rodent toxicity and carcinogenicity studies. The NTP Board of Scientific Counselors was not involved in the determination of the adequacy of the first two year study, but a list of current members of the board is attached as requested.

The protocol for the first sodium fluoride study was developed by the Tracor Jitco Corporation. This organization was responsible for the administration of the NCI bioassay program at that time. The protocol was reviewed and approved by scientists from NCI and the newly formed NTP. I suggest you ask Dr. Griesemer or Upton why your comments were not sought at that time. I have enclosed a copy of the tentative protocol for the second two year study. I would be happy to consider suggestions or criticsm of this research plan.

Sincerely,

John R. Bucher, Ph.D.

Center for
Health Action
Box 1004
Delaware, Ohio 43015

June 27, 1984

Dr. John Bucher
P. O. Box 1233
National Toxixcology Program
Research Triangle Park, NC 27709

Dear Dr. Bucher,

This letter is a request for all the data that has been received as a result of your test regarding the carcinogenic potential of sodium fluoride in experimental animals.

I would also request a complete list of all scientists on your NTP Board of Scientific Counselors and in particular, those who determined that the diet in the fluoride experiments were inadequate.

Furthermore, I'd like to have a list of those who determined the protocol and who approved it, and why my comments on the protocol were not sought as both Dick Greisemer and Arthur Upton, then NCI Director, promised me they would. I would also like to have copies of all the protocols and proposed protocols to date.

I would like to quote the last paragraph of a letter written by Dick Griesemer in 1978:

> Please be assured that the scientists in NCI who will be conducting the experiment on sodium fluoride will insure that the experiment is well-designed, properly conducted, and interpreted without bias. The details of the experiment will be made available to the public and all the data on which conclusions are based will be made freely available in a repository we maintain for that purpose.

In 1977, the National Cancer Institute, under pressure from Congress agreed to complete research on the carcinogenicity of sodium fluoride in rats and mice by 1980.

In 1978, ~~Dr. Yiamouyiannis~~ I was invited to comment on the protocol of the experiments.

As of this date, no results have been released and Dr. Yiamouyiannis has not seen any protocol or any results.

The latest communication I have on this matter is a March 22, 1984 letter from David Rall, Director of the National Toxicology Program who points out that disturbing abnormalties were found which were "clearly not a treatment related effect" and may have been the result of inadequacies in the diet.

He continues:

> At this time we cannot state with certainty that these apparent dietary deficiencies were the cause of the observed clinical signs in the rats. Nonetheless, the problems with the diet were considered serious enough to question the validity of the study as an adequate appraisal of the toxicology and carcinogenicity of NaF. For this reason a second chronic study using an adequate diet has been scheduled, and we anticipate that the new chronic studies will begin in September or October 1984, exposure will be completed in October 1986, and that the Technical Report will likely be issued in early 1988.

Sincerely,

John Yiamouyiannis, Ph.D.
Director

JY/kkm

# Pa. Chief Justice Nix to exit by year-end

## Supreme Court jurist since 1972; Flaherty to get post

By The Associated Press

HARRISBURG — Robert N.C. Nix Jr., who has led the Pennsylvania Supreme Court through some of its more difficult days, has informed his colleagues that he will retire as chief justice, his successor said yesterday.

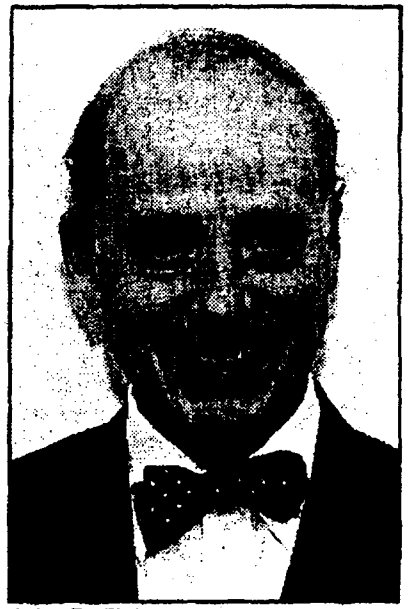
Nix, the first black to head the Pennsylvania Supreme Court, said in a letter to other justices that he planned to step down by the end of the year but did not specify a date, said Justice John P. Flaherty.

Nix, 67, of Philadelphia, would be followed as chief justice by Flaherty, 64, of Indiana Township, who is the most senior of the six associate justices on the state's highest court. The post is filled by seniority.

Nix's retirement plans were reported first yesterday by The Philadelphia Inquirer, which said Nix discussed his decision in an interview.

"I have come to the conclusion that this is the appropriate time to leave," Nix told the newspaper. "Although I loved it very much, it's time for me to do some other things that I've had in mind over the years."

Robert N.C. Nix Jr.



John P. Flaherty

Nix's office said yesterday he would not be available to discuss his plans in the near future.

Nix could serve until 1998, when he would reach age 70, the state's mandatory retirement age for judges. He told the newspaper he made his decision after more than a week of discussions with his family.

He has served on the court since 1972 and has been chief justice since 1984.

Flaherty said it was difficult to express in a few words his thoughts about Nix's retirement.

"I can only say that the chief justice is a very dear friend and, indeed, he is the godfather of my child, and so I will miss him very, very, very much on the court," Flaherty said.

"I think it's too early to describe how things will be when this would occur, but presently the court has a refreshing collegiality," Flaherty said. "Everyone is quite congenial."

Nix's time as chief justice has not always been characterized by good will among members of the court. His tenure has included a grand jury inquiry into the court's affairs and the ouster of Justice Rolf Larsen of Mount Washington, who was convicted of misbehavior in office in an impeachment trial in 1994.

Larsen and other justices traded accusations of wrongdoing, and several justices were called to testify in proceedings against Larsen. Until his removal from the court, Larsen was in line to have been Nix's successor.

"I think he was a real steadying influence during some really tough times for the court," Pennsylvania Bar Association President Art Piccone said of Nix. "I know the Larsen impeachment hurt him, not personally, because he is a very strong man, but for the court."

SEE **NIX,** PAGE A-11

☐ The next chief justice — an eccentric and colorful scholar. **Page A-11.**

# Nix to leave high court

IX FROM PAGE A-1

The actions of Nix himself contributed to the criticism of the upreme Court. A federal judge last ar said Nix committed a "gross use" of his authority by contacting a lower court judge about evidence in a murder trial. The federal dge ordered a new trial after ding that Nix's involvement led to e admission of a secret tape-cording as evidence.

As chief justice, Nix controls the urt calendar and schedules its ssions. It is his responsibility to anage the flow of cases accepted · review by the court.

In 1989, the court decided to ide the chief justice's powers ong the justices. For example, stice Stephen Zappala controls dgeting. In a 1989 interview, Flarty said Nix agreed to the anges to improve operations and nied they were intended as an ack on Nix.

After Nix steps down, Gov. Ridge l name an interim replacement, o would have to be approved by Senate. The seat would come up statewide election next year.

Nix told the Inquirer his office uld send a letter to Ridge "within ys," advising the governor of his ns. He said he might retire by tumn, if his remaining court work complete by then.

The chief justice suffered a head ry in 1991, and there has been culation about his health since n.

# Many speak highly of Flaherty, the next chie

By Jan Ackerman
and Jon Schmitz
Post-Gazette Staff Writers

After a long and colorful legal career, Justice John P. Flaherty Jr. is in line to become chief justice of the state Supreme Court, the highest office in Pennsylvania courts.

"The office of chief justice of Pennsylvania has an enormous amount of responsibility, little in the way of defined duties," Flaherty, 64, said yesterday. He is an Indiana Township resident who, by seniority, will take control of the court after Chief Justice Robert N.C. Nix. Jr. retires later this year.

"It has a tradition that goes back to 1684, an ancient and important office," Flaherty said, reflecting what his colleagues say is his love of law and history.

Flaherty, who began his judicial career on the Allegheny County bench and was appointed to the Supreme Court in 1979, has the most seniority on the court. Next in line is Justice Stephen A. Zappala of Pittsburgh, who joined the Supreme Court in 1983.

Colleagues describe Flaherty as a man with unbounded curiosity and imagination who approaches the law with the eye of a scholar. He is known for his dandy style of dressing, topped by a bow tie. His love of anything Irish is so strong that he even has green stationery.

"He's a typical Irish character," said James I. Smith III, executive director of the Allegheny County Bar Association.

Duquesne University President John E. Murray, a former dean of the University of Pittsburgh Law School, called Flaherty quick-witted and careful about not discussing court business when he's away from the bench.

"He will bring a great imagination as well as a meticulous attention to detail" to the job, Murray said.

"He has an amazing scope of intellectual pursuits. He is interested in history, a perpetual student, not only of the law, but of other disciplines. I think he will make a splendid Supreme Court chief justice."

As chief justice, Flaherty will control the court calendar, preside over conferences and set the court's administrative agenda. He also will represent the court at national conventions and other functions.

Flaherty earned his law degree at Pitt in 1959, rubbing elbows with the likes of Dick Thornburgh, who later would become governor and U.S. attorney general.

Flaherty was teaching at Carnegie Mellon University when he was elected to Allegheny County Common Pleas Court in 1973.

Flaherty became administrative head of the court's civil division, generating headlines and becoming the frequent target of political cartoonists.

He ruled that the city's magistrate court system was unconstitutional, but the state Supreme Court overturned the decision. He said an Oakland woman could not be forced to receive a blood transfusion because it violated her beliefs as a Jehovah's Witness, but Superior Court overturned that decision.

In a decision that received international attention, he ordered the West View Water Authority not to add fluoride to its water supply because he was convinced the chemical would cause cancer.

In 1979, Flaherty won the nominations of both parties for the state Supreme Court and was appointed to the high court by his old law school buddy, Thornburgh.

Flaherty has served on the court during a turbulent era that reached its nadir with the impeachment of Justice Rolf Larsen in 1994. Flaherty did not escape involvement in the Larsen controversy.

In 1982, he was assigned to curtail patronage and spending in the Philadelphia courts, but gave up that responsibility after six months, saying the backing he had received was far less than the total commitment he had been promised. Events during that assignment resulted in Flaherty later being called to testify before a Senate committee conducting Larsen's impeachment trial.

He has not been afraid to take unpopular stances.

In 1992, he wrote the majority opinion throwing out death row inmate Jay C. Smith's conviction in the slaying of Upper Merion teacher Susan Reinert on grounds of prosecutorial misconduct. That decision expanded defendants' protection against double jeopardy in cases of prosecutorial misconduct.

# ef justice

aherty said it was premature to
ict what he would do as chief
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nsibility by the members. I do
hink I would see that changed,"
aid.
aherty lives in Indiana Town-
with his wife, Linet, and their
young children. The judge
he has four other children from
evious marriage.

COMMONWEALTH OF PENNSYLVANIA

SUPREME COURT
SIX GATEWAY CENTER
PITTSBURGH, PENNSYLVANIA 15222

JOHN P. FLAHERTY
JUSTICE

#2

July 31, 1979

Sir Dove-Myer Robinson, Mayor
Auckland, New Zealand

Dear Sir Mayor:

I am in receipt of your letter of July 25, 1979, and thank you for it.

You are correct that I entered an injunction against the fluoridation of the public water supply for a large portion of Allegheny County, Pennsylvania. I did this after a very lengthy series of hearings on the issue. The trial brought into my court experts on the subject of fluoridation, and I meticulously considered the objective evidence. In my view, the evidence is quite convincing that the addition of sodium fluoride to the public water supply at one part per million is extremely deleterious to the human body, and, a review of the evidence will disclose that there was no convincing evidence to the contrary. Since my decision, I have received hundreds of letters, quite a few of which have been sent by physicians and dentists, all concurring with my decision. Contrary to your information, my decree has not been set aside by a higher court. Presently, the issue is on appeal to the Commonwealth Court of Pennsylvania, but the appeal involves merely the jurisdiction of the court--it does not involve the substantative merits of the case.

Prior to my hearing this case, I gave the matter of fluoridation little, if any, thought, but I received quite an education, and noted that the proponents of fluoridation do nothing more than try to impune the objectivity of those who oppose fluoridation. I seriously believe that few responsible people have objectively reviewed the evidence. If you are interested, I suggest that you review the twenty-eight hundred pages of testimony and all of the exhibits presented in this case.

Thank you very much for your inquiry.

Sincerely,

JOHN P. FLAHERTY
Justice
Supreme Court of Pennsylvania

JPF:pld

P.S. I enclose a copy of a letter I received from the Chancellor of Fairleigh Dickinson University, which is representative of the hundreds I have received.

P.S. Since my decision on fluoride, I was elected to the Supreme Court of Pa. J.P.F.

# HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Tuesday, February 6, 1990

Contact: Helen Stopinski
(919) 541-3991

STATEMENT BY DAVID G. HOEL, PH.D.
ACTING DIRECTOR,
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Preliminary data were released February 6, 1990 from a study by this Department's National Toxicology Program on the possibility of a relationship between sodium fluoride and cancer in animals.

The two-year study exposed rats and mice to very high doses of sodium fluoride to determine whether cancers would occur. This standard method enables scientists to detect rare events. At the highest levels, which greatly exceed the amount used in the treatment of water, there were some cases of a form of bone cancer found in the male rats.

These unanalyzed data are essentially the same as those released prematurely several weeks ago. During the next several weeks the NTP staff will prepare a detailed analysis of the data. Outside scientists will review the data and the NTP analysis and present their recommendations at a public meeting in late April.

Until then, the significance of the test results, cannot be determined.

These data resulted from only one study, involving only two species of animals -- rats and mice -- with only five male rats affected by bone cancer (osteosarcoma) and a small number of squamous carcinomas, tumors of the oral cavity, in male and female rats.

In the highest dose, at 79 parts per million, four osteosarcomas were observed among 80 male rats. At 45 parts per million of sodium fluoride, one osteosarcoma was observed in a male rat. The test involved only one of several compounds used in water fluoridation.

(MORE)

In the several hundred pages of pathology data from the test there are also numerous instances of other kinds of tumors and other lesions in both the control animals, who received no sodium fluoride, and in the dosed animals. Some of these may have been due to the age of the rodents in the test.

Within these data tables there are a few statistically positive differences between the dosed and control animals. Any or all of these differences could be the result of chance alone. Their relevance is impossible to determine until the detailed, peer-reviewed analysis of the test is completed.

After 45 years of water fluoridation involving scores of human epidemiological studies both in the United States and in other countries there has not been any evidence that shows a relationship between fluoridation and cancer or other diseases in humans. Moreover, water fluoridation has proven highly effective in improving the nation's dental health by markedly reducing tooth decay.

Fluoride is a natural substance which occurs in some water supplies and foods which humans and animals have ingested from the beginning of time.

The data must be fully analyzed to determine its significance. Until the completion of this process, the many benefits of fluoride warrant continuation of the present policy designed to prevent tooth decay.

The critical matter now is to determine the best scientific judgments possible. That is what this first step by the National Toxicology Program toward the fullest possible study is intended to do.

# # #

JUDGE'S CHAMBERS
COURT OF COMMON PLEAS
PITTSBURGH, PA. 15219

JOHN P. FLAHERTY, JR.
JUDGE

January 5, 1979

Mr. Marno Bevilacqua
New York State Coalition
Opposed to Fluoridation
P.O. Box 263
Old Bethpage, New York 11804

Dear Mr. Bevilacqua:

I sincerely appreciate your letter of December 30, 1978.

Interestingly, although I received quite a bit of flak from the local media, I have received many positive letters from all over the United States.

The hearing before me was quite extensive, lasting approximately seven weeks, and involving quite a bit of scientific testimony regarding fluoridation of the water supply.

After a thorough consideration of the evidence, I believe that fluoridation of the water supply at one part per million is extremely deleterious to the population. Although the media, editorially, insists that my decision is "against scientific concensus," I have received many letters from responsible individuals concurring with my finding.

Once again, thank you.

Sincerely,

John P. Flaherty, Jr.

JOHN P. FLAHERTY, JR.
Presiding Judge - Civil Division

JPF/kbj.

COMMONWEALTH OF PENNSYLVANIA

SUPREME COURT
SIX GATEWAY CENTER
PITTSBURGH, PENNSYLVANIA 15222

JOHN P. FLAHERTY
JUSTICE

July 31, 1979

Sir Dove-Myer Robinson, Mayor
Auckland, New Zealand

Dear Sir Mayor:

I am in receipt of your letter of July 25, 1979, and thank you for it.

You are correct that I entered an injunction against the fluoridation of the public water supply for a large portion of Allegheny County, Pennsylvania. I did this after a very lengthy series of hearings on the issue. The trial brought into my court experts on the subject of fluoridation, and I meticulously considered the objective evidence. In my view, the evidence is quite convincing that the addition of sodium fluoride to the public water supply at one part per million is extremely deleterious to the human body, and, a review of the evidence will disclose that there was no convincing evidence to the contrary. Since my decision, I have received hundreds of letters, quite a few of which have been sent by physicians and dentists, all concurring with my decision. Contrary to your information, my decree has not been set aside by a higher court. Presently, the issue is on appeal to the Commonwealth Court of Pennsylvania, but the appeal involves merely the jurisdiction of the court--it does not involve the substantative merits of the case.

Prior to my hearing this case, I gave the matter of fluoridation little, if any, thought, but I received quite an education, and noted that the proponents of fluoridation do nothing more than try to impune the objectivity of those who oppose fluoridation. I seriously believe that few responsible people have objectively reviewed the evidence. If you are interested, I suggest that you review the twenty-eight hundred pages of testimony and all of the exhibits presented in this case.

Thank you very much for your inquiry.

Sincerely,

JOHN P. FLAHERTY
Justice
Supreme Court of Pennsylvania

JPF:pid

P.S. I enclose a copy of a letter I received from the Chancellor of Fairleigh Dickinson University, which is representative of the hundreds I have received.

COMMONWEALTH OF PENNSYLVANIA

SUPREME COURT
SIX GATEWAY CENTER
PITTSBURGH, PENNSYLVANIA 15222

JOHN P. FLAHERTY
JUSTICE

June 20, 1980

Ms. B.R.G. Murray
P.O. Box 46
Tauranga, New Zealand

Dear Ms. Murray,

Thank you for your letter of June 15, 1980. I'm very happy to hear that you now have the complete transcript which you requested. Actually, the transcript, the exhibits, and my opinion speak for themselves. Regarding, however, your question concerning the continuation of flouridation at the West View Water Authority, more of an explanation is required. At the outset of the case, actually at the request of the plaintiffs, it was agreed that the proceeding would be one for a preliminary injunction, as opposed to a permanent injunction. You, of course, have my opinion and order, and will note that the preliminary injunction was issued and the matter referred to the DER for a complete evaluation. There was an immediate appeal, which, under Pennsylvania Law, stays the effect of an injunction against a political sub-division of the Commonwealth. The DER, later, issued a letter which stated that it had reviewed the matter. I was not satisfied with this purported review, but, before this matter came to adjudication, the plaintiffs agreed that the preliminary injunction had been complied with. I then ruled on preliminary objections which had been filed to the jurisdiction of the court in this case, overruling the preliminary objections. This ruling was immediately appealed, and is presently

on appeal in the Commonwealth Court. The appeal, thus, will determine whether or not DER has exclusive jurisdiction, or whether the Courts of Common Pleas sitting in equity have, at least, concurrent jurisdiction. When this matter has been resolved, and only if it is resolved in favor of at least concurrent jurisdiction in the Common Pleas Court, will there be a hearing on the permanent injunction. As a result, I believe the information regarding a permanent hearing being scheduled for June 11, 1980, is in error.

You sound like a very good person, and, if I ever have the good fortune to visit your beautiful country, I will take pleasure in meeting you personally.

Sincerely,

JOHN P. FLAHERTY
JUSTICE
SUPREME COURT OF PENNSYLVANIA

JPF/dct

COMMONWEALTH OF PENNSYLVANIA

SUPREME COURT
SIX GATEWAY CENTER
PITTSBURGH, PENNSYLVANIA 15222

JOHN P. FLAHERTY
JUSTICE

February 2, 1990

Mr. Eugene Albright
429 Washington Road
North Versailles, Pennsylvania 15137

Dear Mr. Albright:

Thank you for your letter and the items enclosed.

I have been kept abreast of developments in the scientific sphere which more and more focuses on the deleterious effects to the human system which can be traced to ingestion of fluoride. None of this, of course, comes as a surprise to me, but it is refreshing to observe that the subject is receiving legitimate attention.

Very truly yours,

JOHN P. FLAHERTY
JUSTICE
SUPREME COURT OF PENNSYLVNIA

JPF/dct

Note:
ustice Flaherty's 1978 decision o stop fluoridation, was over- urned by a higher court, solely risdictional grounds. Some n it was overturned for other easons. The scientific evidence f harm established in the law- uit remains intact. Justice laherty's 1/5/96 letter sets the ecord straight.

COMMONWEALTH OF PENNSYLVANIA

SUPREME COURT

JOHN P. FLAHERTY
JUSTICE

SIX GATEWAY CENTER
PITTSBURGH, PENNSYLVANIA 15222

January 5, 1996

Ms. Carol S. Kopf
104 Meridian Road
Levittown, New York 11756

Dear Ms. Kopf:

Thank you for your letter. My decision regarding the fluoridation of the public water supply, made during my tenure as a trial judge almost twenty years ago, was, on appeal, purely a jurisdictional issue, thus you are totally correct in your understanding.

Over the years the scientific establishment has taken a more serious interest in the subject of fluoridation than it did at the time I made my ruling. Responsible concerns have been expressed in respected scientific publications, and statistics, then seriously sacrosanct, now questioned. That the practice is deleterious is more and more accepted -- its utility doubted, yet there remain those who promote the practice!

Again, thank you for writing and I hope this answers your inquiry.

Sincerely,

JOHN P. FLAHERTY
Justice
Supreme Court of Pennsylvania

JPF:pdm

Fairleigh Dickinson University
Chancellor's Office
140 Ridge Road
Rutherford, New Jersey 07070
201 · 438-8134
201 · 438-1970

PETER SAMMARTINO
CHANCELLOR

Home

December 19, 1978

The Hon. John P. Flaherty, Jr.
Alleghany County Common Pleas Court
Pittsburgh, Pa. 15219

Dear Judge Flaherty:

Every once in a while a judge makes a watershed decision of great moral import. You have made one in regard to fluoridation. It will take about five years for the turn of events to catch up with the seriousness of your decision.

Having founded a school of dentistry I accepted fluoridation like everyone else and had faith in my faculty, in the A.D.A., in the Public Health Service which made sizable grants to our school.

Then one day I read somewhere that water for kidney machines had to be defluoridated. Since I am prone to kidney stones, the statement aroused my interest. I found that the fluorides combine with the calcium in the body and could cause serious illness or even death.

I began to ask my dentists all of whom are specialists in the field and for whom I have great regard. In a pleasant way they said, "Look Peter, this is not your field. Fluoridation is good and it decreases cavities by 60%."

But I began to read and the more I read the more I became convinced that fluoridation was evil. I began to prod the A.D.A. Again, the cavalier response: "Why everyone knows fluoridation is good. Do you think the Public Health Service would be for it if it wasn't good?"

So I began to poke around in Washington. I ran into a wall of gobbledegook. They pointed majestically to the Kingston-Newburgh experiment. Well, I read the report of that experiment six times. That was the most unscientific and souped-up experiment ever foisted as a breakthrough.

The strange part of it all is that the Department of Agriculture tells farmers not to use fluoridated water, and of course, the F.D.A. forbade the manufacture of pre-natal fluoride tablets.

But even if the case for the 60% decrease had been established (which it hasn't) the fact remains that in the United States and in a number of other countries, it is becoming abundantly clear

that the medical side-effects are most serious.

And then, even if fluoridation were effective and even if there were no side effects, the forced medication is totally repugnant to basic principles.

Now, it is becoming evident that the fluoridated communities have eventually a higher rate of tooth defects than non-fluoridated communities.

I am 74 and it doesn't make too much difference to me, but when I think how every day, in fluoridated communities, we are adding a little poison to bodies knowing full well that some of it (probably about 40%) is cumulative, I cringe at our stupidity.

You probably will find that the greatest decision of your professional career will be that on fluoridation and that should give you the greatest moral satisfaction.

I should like to meet you sometime. Do you ever come to New York? Perhaps we could have lunch or dinner at the University Club.

A Merry Christmas to you.

Sincerely,

Peter Sammartino
Chancellor

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 27709

March 28, 1988

Paul S. Beeber, J.D.
President and General Counsel
New York State Coalition
Opposed to Fluoridation, Inc.
P.O. Box 263,
Old Bethpage, New York, 11804-2363

Dear Mr. Beeber:

Your letter of March 21, 1988, contained several points on which clarification was requested. You requested that I explain an "additional delay" in the 2-year studies of sodium fluoride from previous estimates in earlier correspondence. I believe you are referring to dates derived in early 1984, based on an estimated study start of October, 1984. As indicated in previous correspondence, the actual study start was in October, 1985. The one year delay was due to difficulties encountered in formulating a grain and fish meal based diet with acceptably low background fluoride concentrations, and preparing sufficient diet for the 2-year studies. You may recall that dietary problems were encountered in our previous efforts at studying sodium fluoride, therefore, we did not begin the current study until we were satisfied that all diet problems had been resolved. An additional delay of approximately 6 to 8 months is anticipated because the contract laboratory performing the study has asked for a longer than usual amount of time to process and read the histopathology slides. This is simply because of the large size of the study.

Point 2 concerns the article in Mutation Research (copy enclosed) concerning results of one of our evaluations of the potential genetic toxicity of sodium fluoride. This study is one of a battery of short term assays we routinely perform to evaluate the potential for chemicals to induce damage to the genetic apparatus of cells. These studies are largely confined to looking at effects in cultured cell lines, not in animals. The enclosed paper uses cultured lymphoma cells derived from mice. Sodium fluoride has been found positive in this study, as well as in a number of similar types of studies published by other investigators. These results do not indicate that the chemical in question is a carcinogen. They do, however, point out the need to test the chemical in the 2-year rodent bioassay, which we are doing.

Sincerely,

John R. Bucher, Ph.D.
Carcinogenesis and Toxicologic
Evaluation Branch

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, N.C. 27709

January 18, 1988

Paul S. Beeber, Esq.
New York State Coalition
Opposed to Fluoridation, Inc.
P.O. Box 263,
Old Bethpage, New York, 11804-0263

Dear Mr. Beeber;

I am happy to give you a progress report on the National Toxicology Program's studies on sodium fluoride. The particular study you mentioned, the second chronic toxicity and carcinogenicity study in rodents, was begun in October of 1985. The two-year "in life" portion of the study during which the rats and mice received sodium fluoride at concentrations of 0, 25, 75, or 175 ppm in the drinking water, ended in October of 1987. The animals were then killed, tissues evaluated visually, and skeletal X-rays were taken. No problems were encountered during the conduct of the study. The pathologist overseeing the animal necropsies indicated to me that no unusual types or numbers of tumors were seen in the animals upon gross inspection, and the X-rays did not reveal any bone tumors.

The study is now in the lenghty histopathology phase. Currently, we typically prepare some 40 tissues and organs from each animal for microscopic evaluation. The sodium fluoride study is somewhat larger than most of our other studies and was designed so as to enhance its sensitivity to reveal weak carcinogenic effects. There are 680 animals in this study, necessitating the preparation and evaluation of approximately 27,000 microscope slides. The data preparation and evaluation phases typically take 2-3 years, and sometimes longer if there are large numbers of either neoplastic or nonneoplastic lesions observed. At this time I simply cannot give you an estimated date for the ultimate publication of this study. Preliminary results from the microscopic evaluations are available to the public once the diagnoses have been approved by a pathology peer review panel which is convened to evaluate the results.

Sincerely,

John R. Bucher, Ph.D.
Carcinogenesis and Toxicology
Evaluation Branch, NTP

# HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR IMMEDIATE RELEASE
Thursday, April 26, 1990

Contact: Sandra Lange
(919) 541-3201

STATEMENT BY DAVID P. RALL, M.D., PH.D.
DIRECTOR
NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Today, April 26, 1990, the National Toxicology Program's (NTP) Board of Scientific Counselors' Technical Reports Review Panel met in Research Triangle Park, North Carolina. This group of non-HHS scientists reviewed and discussed in public forum the results of recent NTP studies in animals on the toxicity and carcinogenicity of sodium fluoride.

In its evaluation of the NTP studies on sodium fluoride, the Panel agreed with the NTP that the evidence for bone tumor formation in male rats was too weak to be attributed to fluoride administration. To support their evaluation, the Panel noted that the bone tumor effect was not found in mice or in female rats receiving the same dose levels and that the increase in the numbers of affected male rats was small. Thus, the possibility that the marginal increase could have occurred by chance could not be ruled out. For these reasons, the Panel concurred with the NTP conclusions of "equivocal evidence of carcinogenic activity" in male rats and "no evidence of carcinogenic activity" in female rats or in male and female mice.

Estimating potential risks to humans from fluoride exposure requires analyses of all the available information in addition to those reported today by the NTP, both experimental and epidemiological. Now that these NTP studies have been peer reviewed by the external peer review group, the results can be considered by the HHS as part of the Department's wider analysis of the appropriate use of fluorides in human health.

The Department's analysis is being conducted under the leadership of Dr. Frank Young, the Deputy Assistant Secretary for Health, Science and Environment. Dr. Young's group, a subcommittee of a PHS Committee to Coordinate Environmental Health and Related Programs, has underway a thorough examination of scientific, peer-reviewed studies of the risks and benefits of fluorides.

*Attached is the NTP "Explanation of Levels of Evidence."

COMMONWEALTH OF PENNSYLVANIA

SUPREME COURT
SIX GATEWAY CENTER
PITTSBURGH, PENNSYLVANIA 15222

JOHN P. FLAHERTY
JUSTICE

August 30, 1983

Dr. Stephen A. Dean, D.C., President
Massachusetts Communities for Pure Water, Inc.
1367 Parker Street
Springfield, Massachusetts 01129

Dear Dr. Dean,

I received and read your letter this morning regarding a case I handled some years ago. In answer to your first question, yes, as a Judge of the Court of Common Pleas of Allegheny County, I presided over a lengthy trial which resulted in my entering an injunction against the fluoridation of the public water supply for a large portion of Allegheny County, Pennsylania.

The answer to your second question, of course, is not as simply stated as the answer to the first. Although the conclusions which I reached leading to the entry of the decree would be set forth in my opinion, reflecting on the matter at this late date, I see that my opinion did not do the subject the justice it deserved. The record developed in the trial before me consisted of approximately 2,800 pages, and, since that time, there have been many developments, both empirical and statistical which bear on the subject. In essence, my conclusion was that there is strong, indisputable evidence that fluoridation, even at 1 p.p.m., is extremely deleterious to the human system. It appears as though responsible evidence is being ignored, or, even



worse, superficially impugned as "unfounded" and "unreliable". I saw it otherwise. My decree called for an unbiased and independent inquiry into this most serious matter. I remain of that view. The case then before me, at least directly, did not involve question of the propriety of government injecting an agent into the water supply which admittedly is not for the

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I hope the foregoing answers your inquiry, and I enclose herewith a copy of my opinion along with several other items representative of thousands of pieces of correspondence which I have received from around the world on this subject.

Very truly yours,

JOHN P. FLAHERTY
JUSTICE
SUPREME COURT OF PENNSYLVANIA