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Background Materials for Hansson and Roos (1987)

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The Effect of Fluoride and Calcium on Spinal Bone Mineral Content: A Controlled, Prospective (3 Years) Study

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Summary. Daily treatment with 30 mg of sodium fluoride (NaF) and 1 g of calcium over a 3-year period increased the bone mineral content (BMC) in the spines of women (n = 25) with osteoporosis. Determination of the BMC was followed with dual photon absorptiometry (^{137}Cs-^{241}Am) in the third lumbar vertebra. No increase in BMC was found with only 10 mg sodium fluoride in combination with calcium (n = 25), with calcium alone (n = 25), or with placebo (n = 25). No serious side effects were registered. There was, however, minor gastrointestinal distress in one-fifth of the patients taking 30 mg NaF daily.

Key words: Absorptiometry — Calcium — Osteoporosis — Fluoride — Fracture.

Fluoride has been given to humans based on the hypothesis that it stimulates formation of new bone which is normally mineralized if sufficient calcium is provided. Most (60–70%) osteoporotic women respond to fluoride without side effects and studies have shown an increase of bone mass (up to 30–50% in 1 year) and a tenfold decrease of fractures [1–9]. However, these studies have used high doses of NaF (50–80 mg/day), which induce significant side effects, and have not included control groups. Since we, in an earlier trial, found the same effect on the BMC of the spine after medication with 50 mg NaF as with 30 mg NaF daily, this study examined the effect of lower doses of fluoride in women with idiopathic osteoporosis [5].

Materials and Methods

Women (n = 100) selected for this study had at least one and a maximum of three vertebral compression fractures within the thoracic or lumbar spines, sustained during minor traumas. Since L3 was the vertebral level used for determination of the spinal bone mineral, a fracture at this level excluded from the study. All the women were postmenopausal, and none had known diseases or was taking a medication that could directly influence the normal skeletal metabolism.

The mean age of the women was 66 (SD 6) years. They were randomly placed into four different treatment groups (A, B, C, and D), each made up of 25 women. The mean age of the women in each group and treatment given is presented in Table 1.

Fluoride was given as sodium fluoride. It was administered in capsules containing 30 (Group A) or 10 mg each (Group B). Calcium was given to both of these groups, and to another that did not receive fluoride (Group C), as a combination of bicarbonate, lactate, and gluconate, 1 g/day. The patients in group D got one daily capsule containing placebo (starch). The patients receiving fluoride took it in the morning and the calcium in the evening.

Roentgenograms of the lumbar and thoracic spines were taken within 1 month after the treatment started and again after three years of treatment. The changes in the BMC of the third lumbar vertebra (L3) were followed with dual photon absorptiometry [12, 13]. BMC was determined at the start of the treatment, at 1 year, 1½ years, 2 years, and 3 years of treatment. Our dual photon absorptiometer uses two radionuclides with different gamma energies (^{241}Americium and ^{137}Cesium) arranged so there is a common collimated radiation beam. The transmitted radiation of both energies is measured with a scintillation detector and nuclear counting instrumentation. The radiation beam is centered over the L3 using an X-ray tube and an image intensifier. Transmission measurements are then performed as a scanning procedure over the vertebra in 4 mm steps. By plotting the attenuated energies at each step, a bone profile curve is obtained from which the BMC is calculated. The stability of the absorptiometer, which is of crucial importance for a high reproducibility especially in a study extended over several years, has been

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Table 1. Changes in osteoporotic women of BMC (g/cm) in L3 over 3 years treatment

Group	Age	Treatment NaF	Ca	Year 0	1.0	1.5	2.0	3.0
A	65.2	30	1	2.72	2.94	2.97	3.09[a]	3.18[b]
B	66.4	10	1	2.75	2.77	2.78	2.75	2.83
C	64.6	0	1	2.69	2.68	2.74	2.74	2.68
D	67.2	placebo		2.75	2.81	2.73	2.72	2.67

Comparisons were made with the initial BMC value
[a] $P < .05$
[b] $P < .01$

tested by 57 measurements of the same Al-phantom over a period of 5 years. The 57 measurements gave a regression line with a slope that differed 0.15% from a straight line [10]. The accuracy of our method has been determined in numerous vertebrae before and after they have been ashed. The accuracy has also been determined by measurements first of vertebrae *in situ* in the body and then after they have been excised from the body. In these experiments the errors in accuracy and reproducibility have been found to be less than 3% [10–12]. A more detailed description of the theory and the measuring technique has been given earlier [11, 12].

Results

The BMC changes in the four different groups are presented in Table 1.

The number of patients who completed the 3-year study were 24 in Group A, 23 in Group B, 22 in Group C, and 19 in Group D. There were no statistically significant changes in the BMC in groups B, C, or D. Group A increased significantly ($P < 0.01$). The absolute increase in BMC in Group A was 0.46 g/cm, which corresponded to a 17% increase over the 3 years of treatment.

The increase of BMC in Group A was statistically significant after 1½ years of treatment, with a majority of the women showing an increase. After 3 years, 19/25 showed an increase, 5/25 showed a decrease. The biggest individual increase over 3 years was 27.1%, while the biggest individual decrease was 4.2%. The mean increase among the responders in Group A was 18.5%. The corresponding decrease among the nonresponders in the same group was 2.2%. The individual changes in Group A are shown graphically in Figure 1. Five of the patients in Group A had adverse reactions probably caused by the treatment. Four had mild gastrointestinal symptoms (nausea and gastritis). One patient developed a peptic ulcer which forced her to abandon the treatment after 10 months. Two of the women with adverse reactions belonged to the nonresponders. Four certainly new vertebral compression fractures were noticed in the entire group of women; two occurred in Group B and one in Groups C and D respectively.

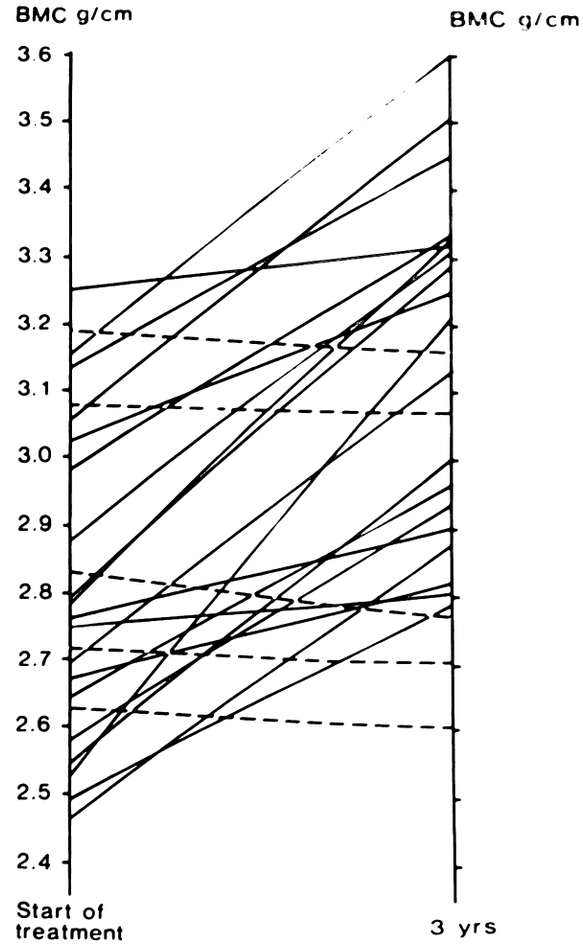

Fig. 1. The individual changes in BMC in group A during 3 years' treatment with 30 mg NaF and calcium. The dotted lines represent the 5 subjects who did not respond to this treatment.

Discussion

This controlled, prospective study indicated that 30 mg of sodium fluoride and 1 g calcium taken daily significantly increased the BMC in the lumbar spine. The average value after 3 years of treatment among the women in group A was in the lower portion of the normal range for age-matched normals. This increase was not found when only 10 mg sodium fluoride or only calcium was given daily. Pending that the increase of BMC reflected an apposition of bone with normal qualities, the increase of BMC in those 76% who did respond in Group A probably could be of a sufficient magnitude (18.5%) to lower the risk of new fractures due to minor traumas. In another study [14] we found that a BMC deficit of about 15–20% was associated with

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an apparent risk of the first vertebral fracture in women of this age; fluoride treatment over only 3 years put a majority of the responding subjects above this threshold.

A lower incidence of compression fractures after fluoride/calcium treatment has been reported from studies in osteoporotic patients [2, 4, 10]. As in these earlier studies, however, not all individuals respond to fluoride treatment and there are some mildly adverse side effects even at low doses. The lack of response may reflect lack of bone cell activity, an absence of precursor bone cells, or a simple failure to elevate blood fluoride levels (possibly associated with noncompliance in those with side effects). Some studies [2, 3] have failed to show positive responses to fluoride on the predominantly compact bone (75%–95%) of the distal radius (even in patients who responded vigorously in iliac crest biopsy [2]), but this discrepancy from our results could be explained, for example, by a difference in effectiveness of this agent on trabecular bone of the axial skeleton. As with previous studies on compact bone, however, no effect of calcium supplementation was evident in the spine. Given the normal calcium intake of Swedish patients (about 800 mg/day), it is not clear if the calcium provided with the fluoride therapy is necessary in this population, thought it may be of value in the populations where a lower dietary intake provides insufficient mineralization resources for the fluoride-induced bone.

Acknowledgments. The study was supported by the Swedish Medical Research Council (17X-6576) and Asker's Foundation.

References

1. Baylink DJ, Bernstein DS (1967) The effects of fluoride therapy on metabolic bone disease: a histologic study. Clin Orthop 55:51–85
2. Briancon D, Meunier PJ (1980) Le fluor en pathologie et en thérapeutic osseuses: son application au traitement des ostéoporoses. Lyon Med 243:183–94
3. Christiansen C, Christiansen MS, McNair P, Hagen C, Stocklund KE, Transboel I (1980) Prevention of early postmenopausal bone loss. Eur J Clin Invest 10:273–279
4. Franke J 1978 Our experience in the treatment of osteoporosis with relatively low sodium fluoride doses. In: Courvoisier B, Donath A, Baud CA (eds) Fluoride and bone. Hans Huber Publishers, Bern, Switzerland, pp 238–241
5. Hansson T, Roos B. (1978) Osteoporoses. Effect of combined therapy with sodium fluoride, calcium and vitamin D on the lumbar spine in osteoporosis. AJR 126:1294–1297
6. Jowsey J, Riggs BL, Kelly PJ, Hoffman DL (1972) Effect of combined therapy with sodium fluoride, vitamin D and calcium in osteoporosis. Am J Med 53:43–49
7. Reutter FW, Olah AJ (1978) Bone biopsy findings and clinical observations in long-term treatment of osteoporosis with sodium fluoride and vitamin D. In: Courvoisier B, Donath A, Baud CA (eds) Fluoride and bone. Hans Huber Publishers, Bern, Switzerland, pp 249–255
8. Riggs BL, Hodgson SF, Hoffman DL, Kelly PJ, Johnson KA, Taves D (1980) Treatment of primary osteoporosis with fluoride and calcium. JAMA 243:446–449
9. Riggs BL, Seeman E, Hodgson SF, Taves DR, O'Fallon WM (1982) Effect of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal osteoporosis. N Engl J Med 306:446–450
10. Ringe JD, Kruse HP, Kuhlencordt F (1978) Ergebnisse einer Langzeittherapie der primären Osteoporose mit Natriumfluorid. Dtsch Med Wochenschr 103:248–252
11. Roos BO, Sköldborn H (1974) Dual photon absorptiometry in lumbar vertebrae. I. Theory and method. Acta Radiol 3:266–280
12. Roos BO (1975) Dual photon absorptiometry in lumbar vertebrae. II. Precision and reproducibility. Acta Radiol 3:291–303
13. Roos B, Hansson T (1980) Dual photon absorptiometry in lumbar vertebrae. An experimental study of the baseline error. Acta Radiol 19:111–114
14. Hansson T, Roos B (in press) The bone mineral content of the lumbar spine at the occurrence of the first vertebral crush fracture. Clin Orthop

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EPA Reviewer: Jaime D'Agostino **Signature:**
Risk Assessment Branch II, Health Effects Division (7509P) **Date:** 12/23/14
EPA Secondary Reviewer: Karlyn Middleton/Ray Kent **Signature:**
Risk Assessment Branch II (KM) and Immediate Office (RK), Health Effects Division (7509P) **Date:** 12/23/14
Template version 09/11

TXR#:

DATA EVALUATION RECORD

STUDY TYPE: Controlled prospective study in humans; non-guideline

PC CODE: 075202 **DP BARCODE:** N/A

TEST MATERIAL (PURITY): Sodium fluoride (purity was not reported).

SYNONYMS: N/A

CITATION: Hansson, T., and B. Roos (1987) The effect of fluoride and calcium on spinal bone mineral content: A controlled, prospective (3 years) study. Sahlgren's Hospital, University of Gothenberg, Sweden, Calcified Tissue International 40:315-317.

SPONSOR: N/A

EXECUTIVE SUMMARY:

In a controlled prospective study in humans (MRID 49489102), 100 postmenopausal women, with between 1 and 3 vertebral compression fractures, were placed into four treatment groups (25 per group) and given fluoride (sodium fluoride capsule) and/or calcuim (combination of bicarbonate, lactate, and gluconate) daily over a 3 year period. Group 1 was given 30 mg/day sodium fluoride (13.6 mg F/dose) and 1 g/day calcium, Group 2 was given 10 mg/day sodium fluoride (4.5 mg F/dose) and 1 g/day calcium, Group 3 was only given 1 g/day calcium, and Group 4 was given starch as a placebo (capsule). The mean age of the women in the study was 66±6 years. Changes in bone mineral content (BMC) of the third lumbar vertebra (L3) were measured by dual photon absorptiometry at the start of treatment and then again at 1 year, 1.5 years, 2 years, and 3 years.

Following exposure to 30 mg sodium fluoride (+ calcium), 5 women had adverse reactions consisting of nausea and gastritis in 4 women and a peptic ulcer in 1 woman. No adverse reactions were seen in the other dose groups. No statistical analysis for the adverse effects were performed by the study authors; however, EPA has done an analysis to compare the proportion of subjects who experienced adverse reactions between the 30 mg sodium fluoride dose level group and the placebo group (0 mg sodium fluoride). The result indicates that the proportion of subjects who experienced adverse reactions in the 30 mg sodium fluoride dose level group was significantly higher than that of the placebo group (20% vs. 0%, Exact-test p-value = 0.05).

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BMC of the women in the group receiving 30 mg sodium fluoride (+ calcium) was slightly elevated after 1 and 1.5 years and was significantly increased at the 2 and 3 year BMC measurements. The mean increase was 18.5%. This suggests that fluoride may stimulate formation of new bone. No treatment-related changes in BMC were seen in women given 10 mg/kg/day (+ calcuim), calcium alone, or the placebo.

The LOAEL is 30 mg sodium fluoride/day (13.6 mg F/dose), based on gastrointestinal symptoms (nausea and gastritis). The NOAEL is 10 mg sodium fluoride/day (4.5 mg F/dose).

This controlled prospective study in humans is acceptable/non-guideline.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were not provided.

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I. MATERIALS AND METHODS:

A. MATERIALS:

1. **Test material:** Sodium Fluoride

Description: none

Lot/batch #: **Not reported**

Purity: **Not reported**

Compound stability: **Not reported**

CAS # of TGAI: 7681-49-4

Structure: NaF

2. **Vehicle and/or positive control:** Capsule.

3. **Subjects:**

Sex: 100 postmenopausal females with 1-3 vertebral compression fractures within the thoracic or lumbar spine

Age: 66 ± 6 years

B. STUDY DESIGN:

1. **In life dates:** Not reported.

2. **Subject assignment and dosing:** The subjects were randomly divided into four groups (Table 1). Group A was administered 30 mg of sodium fluoride in capsule form per day and 1 g/day of calcium as a combination of bicarbonate, lactate, and gluconate per day; group B was administered 10 mg sodium fluoride in capsule form and 1 g/day calcium as a combination of bicarbonate, lactate, and gluconate per day; group C was administered 1 g/day calcium as a combination of bicarbonate, lactate, and gluconate alone per day; and group D was administered a placebo capsule of starch per day. Sodium fluoride was taken in the morning and calcium was taken in the evening.

Table 1. Study design.

Group	Age	Sodium fluoride (mg/day) [mg F/dose]	Calcium (g/day)
A	65.2	30 [13.6]	1
B	66.4	10 [4.5]	1
C	64.6	0	1
D	67.2	placebo	0

C. METHODS:

1. **Bone Mineral Content (BMC):** Changes in BMC of the third lumbar vertebra (L3) were measured by dual photon absorptiometry at the start of treatment and then again at 1 year,

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1.5 years, 2 years, and 3 years.

2. **Statistics:** No description of the statistical methods used were described in the study.

II. RESULTS:

1. **Clinical Signs:** Five subjects in group A (30 mg sodium fluoride) had an adverse reaction. This manifested as nausea and gastritis in four patients. The fifth patient developed a peptic ulcer which resulted in her abandoning treatment after 10 months. EPA has done an analysis to compare the proportion of subjects who experienced adverse reactions between the 30 mg sodium fluoride dose level group and the placebo group (0 mg sodium fluoride). The result indicates that the proportion of subjects who experienced adverse reactions in the 30 mg sodium fluoride dose level group was significantly higher than that of the placebo group (20% vs. 0%, Exact-test p-value = 0.05).

2. **BMC:** The group treated with 30 mg sodium fluoride and calcium (Group A, Table 2) had statistically significant increases in BMC at the 2 and 3 year measurements. After 3 years, 19 out of the 25 women showed an increased BMC. The mean increase in BMC was 18.5%.

Table 2. Changes in BMC (g/cm) in L3.

Group (sodium fluoride)	BMC (g/cm)				
	0 years	1 year	1.5 years	2 years	3 years
A (30 mg)	2.72	2.94	2.97	3.09[a]	3.18[b]
B (10 mg)	2.75	2.77	2.78	2.75	2.83
C (0)	2.69	2.68	2.74	2.74	2.68
D (placebo)	2.75	2.81	2.72	2.72	2.67

[a] P<0.05
[b] P<0.01

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: The investigators concluded that the adverse reactions were probably caused by the treatment. The investigators also concluded that 30 mg of sodium fluoride and 1 g of calcium taken daily significantly increased the BMC in the lumbar spine. Treatment with 10 mg of sodium fluoride in combination with calcium, calcium alone, or the placebo did not result in increased BMC.

B. REVIEWER COMMENTS: Based on the lack of information regarding timing, frequency, and severity of the gastrointestinal effects it is difficult to determine if the effects are the result of an acute or repeated exposure. However, the reviewer does believe that the nausea, gastritis, and peptic ulcer are treatment-related. It is possible that the nausea and gastritis are due to acute exposure since the effects observed are consistent with the known toxicity caused by fluoride following acute exposure (animals and humans). Additionally, fluoride is rapidly absorbed from

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the gastrointestinal tract (half-life of about 30 minutes). The peptic ulcer observed in the high dose group in one subject at 10 months is likely not the result of acute exposure to fluoride. It is possible that other gastrointestinal effects were present prior to the formation of an ulcer, or the fluoride treatment could have worsened a previously unidentified ulcer. However, based on the lack of information in the study, the reviewer feels the ulcer should not be considered treatment related since it only occurred in one individual. Based on the available information, it is unclear whether repeated exposure over the three year period led to an increase in severity of frequency of toxicity. No effects were observed in the lower fluoride treatment group, calcium only group, and placebo group.

The reviewer agrees with the conclusion regarding the effects of fluoride on BMC; however, this is a beneficial (non-adverse) effect of fluoride and not relevant for choosing the point of departure. The NOAEL for this study is 10 mg sodium fluoride/day (equivalent to 4.5 mg F/dose). The LOAEL is 30 mg sodium fluoride/day (equivalent to 13.6 mg F/dose) based on gastrointestinal symptoms.

C. STUDY DEFICIENCIES: It is not clear from the study report when the observed gastrointestinal symptoms occurred, how often they were observed, or whether they became worse with repeated exposure. A peptic ulcer was observed after 10 months in one individual; however, it is not clear if she experienced early signs of gastrointestinal symptoms prior to the ulcer. This makes it difficult to discern if the effect was actually treatment-related, the result of an acute exposure, or the result of repeated exposure.

Calcium was given along with fluoride in this study. Calcium is known to be able to bind fluoride resulting in formation of calcuim fluoride which is poorly absorbed in the gastrointestinal tract. Based on the rapid absorption of fluoride and that calcium was taken in the evening while fluoride was taken in the morning, it is likely that this was not a confounding factor.

The information reported in the study was limited; for example no information on purity and minimal information on the vehicle were reported. There is very limited details on how they assured the patients were complying with the assigned treatment and how the side effects were monitored. Finally, the population of this study was focused (postmenopausal women with a mean age of 66 ± 6 years and 1-3 vertebral compression fractures within the thoracic or lumbar spine) and may not be representative of the entire human population.

The deficiencies do not change the conclusion of the study that gastrointestinal symptoms were observed following treatment with sodium fluoride. However, they do present some uncertainties which must be considered when interpreting the results.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

December 29, 2014

MEMORANDUM

SUBJECT: Ethics Review of Human Toxicity Study with Fluoride

FROM: Kelly Sherman, Human Studies Ethics Review Officer
Office of the Director
Office of Pesticide Programs

TO: Christina Swartz, Chief
Risk Assessment Branch II
Health Effects Division
Office of Pesticide Programs

REF: Hansson, T. and Roos, B. (1987). The Effect of Fluoride and Calcium on Spinal Bone Mineral Content: A Controlled, Prospective (3 Year) Study. Sahlgren's Hospital, University of Gothenberg, Sweden. *Calcified Tissue International.* 40:315-7. (MRID 49489102)

I have reviewed the referenced human toxicity study with fluoride. I conclude that if the study is determined to be scientifically valid and relevant, there is no regulatory barrier to EPA relying on this research in actions taken under FIFRA or §408 of FFDCA.

Summary Characteristics of the Research

In this study, 100 postmenopausal women were placed into four treatment groups (25 per group) and given fluoride and/or calcium daily over a 3-year period. Group 1 was given 30 mg/day sodium fluoride (13.6 mg fluoride/dose) and 1 g/day calcium, Group 2 was given 10 mg/day sodium fluoride (4.5 mg fluoride/dose) and 1 g/day calcium, Group 3 was given 1 g/day calcium, and Group 4 was given starch as a placebo (capsule). The mean age of the women in the study was 66±6 years. Changes in bone mineral content of the third lumbar vertebra (L3) were measured by dual photon absorptiometry at the start of treatment and then again at 1 year, 1.5 years, 2 years, and 3 years.

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1. **Value of the Research to Society:**

The objective of this study was to investigate the changes in bone mineral content as a result of receiving doses of fluoride and calcium that were lower than those shown to increase bone mass and decrease fractures in earlier studies. The researchers also collected information about adverse reactions or side effects. The study was conducted at Sahlgren's Hospital, University of Gothenberg, Sweden. The results were published in *Calcified Tissue International* in 1987. The study was partially funded by grants from the Swedish Medical Research Council and Asker's Foundation. EPA is proposing to use the study in its assessment of the acute dietary risks of fluoride residues that result from some uses of the fumigant sulfuryl fluoride.

2. **Subject Selection**:

a. Demographics. One hundred female subjects (mean age 66±6 years) participated in the study.

b. Pregnancy and Nursing Status. The subjects were postmenopausal and therefore not pregnant or nursing.

c. Recruitment. There is no information about how the subjects were recruited, but it is likely that they were patients who had been treated at Sahlgren's Hospital for vertebral compression fractures.

3. **Risks and Benefits**:

a. ***Risks.*** There is no information about how the potential risks were evaluated nor whether the risks were explained to potential subjects before they agreed to participate. The article notes that the highest dose of fluoride in the study (30 mg fluoride) was equal to the amount of fluoride potentially swallowed by children following prophylactic dental treatment with fluoride gel (30 mg fluoride), so presumably the dose level was considered safe at the time.

b. Benefits. There are no benefits to the subjects.

c. ***Risk-Benefit Balance.*** There is no information about the risk-benefit balance. The researchers may have considered the potential societal benefits of increased understanding of fluoride effects to have outweighed the risks associated with the study because the highest dose level of fluoride (30 mg) was likely considered safe because previous studies were conducted with higher doses, although it is noted in the article that the higher doses in the other studies "induce[d] significant side effects."

4. **Independent Ethics Review**: There is no information about whether the study underwent independent ethics review.

5. **Informed Consent**: There is no information about whether the subjects provided informed consent.

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6. **Respect for Subjects.** There is no information about whether subjects were compensated for participating, or whether they were afforded the right to withdraw from the study at any time. The subjects' identifies are not revealed in the study report.

Applicable Standards

Standards Applicable to the Conduct of the Research

The portions of EPA's regulations regarding the conduct of research with human subjects, 40 CFR part 26 subpart A - L, do not apply since the research was neither conducted nor supported by EPA, nor was it conducted by a person with the intention to submit the results to EPA.

This research was conducted in Sweden in the early 1980s by physicians in the Department of Orthopedic Surgery (Hansson) and the Department of Radiophysics (Roos) at Sahlgren's Hospital. In the 1980s in Sweden, independent ethics review of biomedical research would have been prevalent (Solbakk, 1991; Attachment 1). Ethics review committees were first established in Sweden in 1965, and by 1978 the Swedish Medical Research Council proposed mechanisms for formalizing the research ethics committee system in Sweden (Solbakk, 1991). The principles applied by the committees likely would have derived from commonly accepted international principles of research ethics such as those articulated in the Declaration of Helsinki (Solbakk, 1991). Current laws and regulations governing the conduct of human research in Sweden were not in place in the 1980s.

Standards Applicable to the Documentation of the Research

EPA identified this study through a review of the public literature. No person has independently submitted the published article or any results of this research to EPA. Consequently, the requirements for the submission of information concerning the ethical conduct of completed human research contained in EPA regulations at 40 CFR part 26, subpart M do not apply.

Standards Applicable to EPA's Reliance on the Research

The Agency's rule (40 CFR part 26 subpart Q) defines standards for EPA to apply in deciding whether to rely on research—like this study—involving intentional exposure of human subjects. The applicable acceptance standards from 40 CFR part 26 subpart Q are these:

> **§26.1703.** Except as provided in **§**26.1706, EPA must not rely on data from any research subject to this subpart involving intentional exposure of any human subject who is a pregnant woman (and therefore her fetus), a nursing woman, or a child.
>
> **§26.1704** EPA must not rely on data from any research subject to this section if there is clear and convincing evidence that: (1) The conduct of the research was fundamentally unethical (e.g., the research was intended to seriously harm participants or failed to obtain informed consent); or (2) The conduct of the research was deficient relative to the ethical standards prevailing at the time the research was conducted **in a way that placed**

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participants at increased risk of harm (based on knowledge available at the time the study was conducted) or impaired their informed consent.

EPA has submitted this study for review by the Human Studies Review Board (HSRB) because 40 CFR §26.1602 requires HSRB review for pre-2006 studies intended for EPA reliance that were conducted for the purpose of identifying or measuring a toxic effect. This study meets those criteria.

Compliance with Applicable Standards

All of the subjects in this study were postmenopausal women (mean age was 66±6 years). Thus, all of the subjects were adults and none were pregnant or nursing. EPA's reliance on the research is therefore not prohibited by 40 CFR §26.1703.

With regard to 40 CFR §26.1704 (whether there was clear and convincing evidence that this research was either fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent), there is no relevant information in the published article. I tried several different approaches to locate records of an ethics review or any other information about the ethical conduct of this study, but I was not successful in that regard.

I attempted to obtain information about this study from the Swedish Medical Research Council, Sahlgrenska University Hospital, and the Regional Ethics Review Board for Gothenburg, but either received no response or was notified that there was no information available because of the date of this study.

Based on the absence of clear and convincing evidence that the research was fundamentally unethical or intended to harm participants, I conclude that reliance on the research is not prohibited by 40 CFR §26.1704(1). Based on the absence of clear and convincing evidence that the research was deficient relative to the prevailing ethical standards, I conclude that reliance on the research is not prohibited by 40 CFR §26.1704(2).

Conclusion

I find no barrier in law or regulation to reliance on MRID 49489102 in EPA actions taken under FIFRA or §408 of FFDCA. I defer to others for a full review of the scientific validity of this study. If it were determined not to have scientific validity, it would also not be ethically acceptable.

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Appendix 1:

Ethics Review Committees [in Biomedical Research] in the Nordic Countries: History, Organization, and Assignments (Solbakk, 1991)

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ETHICS REVIEW COMMITTEES [IN BIOMEDICAL RESEARCH] IN THE NORDIC COUNTRIES: HISTORY, ORGANIZATION, AND ASSIGNMENTS

JAN HELGE SOLBAKK, M.D., Th.M.

Introduction.

"You Nordic people all look similar. You all have the same names, and you all live in countries too small to be of any general interest". This somewhat provocative statement by a well-known American psychiatrist attending a conference in bioethics in summer 1990 could serve as one motivation for trying to provide an accurate description of the ethics committee systems in the Nordic countries. The description is limited to *three* Nordic Countries -- Sweden, Denmark, and Norway, representing three *different* ways of organizing regional and national bodies that address issues in medical ethics. My hope is to show that even in small countries with close cultural relations there is room for plurality in the field of medical ethics.

Regional Ethics Review Committees: History, Organization, and Assignments.

1. Sweden.

In the early 1960s a discussion started in Sweden about setting up Regional Ethics Review Committees (REC) that addressed medical research involving human subjects. The first committee was established in 1965 at the Karolinska Hospital in Stockholm. The process of establishing ethics review committees in all the medical faculties was hastened by the 1966 NIH decision that: NIH-associated medical research projects involving human subjects should undergo review by a research ethics committee. In order to ensure review of all research projects, the Medical Research Council, in 1978, proposed mechanisms for formalizing the research ethics committee system in Sweden. The six existing RECs are appointed by the University Boards and by the principal hospital authorities in the region, each REC consisting of approximately 2-3 lay members and 10 professional biomedical researchers. Besides reviewing research projects, the RECs initiate measures to provide teaching in the subject area of research ethics and

to provide information on the subject to hospital staff and hospital authorities.

2. Denmark.

The Danish system of *seven* Regional Scientific-Ethical Review Committees (R-SERC), established in 1978, is characterized by *parity* of lay members and researchers. The 3 researchers on each committee are appointed by the Danish Medical Research Council, while the lay members are appointed by the county council of the region in question. "The committees cover all biomedical research projects within their region, comprising medicine, dentistry and pharmacy research, conducted in hospitals, research institutions, industrial undertakings, universities, or within the primary health service" (1, p. 156).

All decisions of the R-SERCs must be *unanimous*, otherwise the projects in question must be referred to the Central SERC (see below).

3. Norway.

The National Health Service in Norway is divided into *five* regions with 600,000 to 1.2 million inhabitants, and a university hospital in each region. About 80% to 90% of all patient-related biomedical research is carried out at the universities, mainly with financial resources from the university itself and/or the Norwegian Medical Research Council (MRC), but with substantial additional contributions from private Cancer and Heart Associations. The pharmaceutical industry supports trials of medical preparations, which constitute about 60% of the patient-related biomedical projects presented to the RECs.

The organization of the Regional Ethics Review Committees in Norway corresponds to that of the National Health Service, so that there are *five* RECs administered by the medical faculties of the universities.

The **members** of the RECs are appointed by the Ministry of Education and Research to which they also report. Their current support is provided by the Ministry, which also provides the salary for the secretaries of each REC. The budget as well as the activities of the committees are administered by the medical faculties. The committees report once a year to the Ministry of Education and Research.

The RECs have seven members: a medical professional recommended by the medical faculty of the region; a medical professional recommended by the official health authorities of the region; a nurse; a member from the regional hospital owners; a

member with competence in *ethics;* an attorney, and a lay representative. The Ministry of Education and Research appoints the chairmen and the vice-chairmen. The members are appointed for *four* years and can be re-elected once. The two main responsibilities of the REC are *advisory* and *guiding* functions in matters of research ethics, and *providing information* on the principles of research ethics.

The guidance and advisory activities are based upon commonly accepted principles of research ethics with due concern to guidelines established by national or international bodies, such as the revised Helsinki Declaration. The transactions of the committees are not open to the public. All relevant projects in biomedical research in the respective regions are subject to review by the RECs. Multicenter studies are reviewed by the regional REC where the project organizer is located. The REC *recommends* that a project can or should not be carried out; the project can not start until it has been reviewed by the REC.

The REC meets about every six weeks. Approximately 1-2% of the projects are not recommended by the committees. There is no central body of *appeal* (see below).

National/Central Bodies in Medical Ethics: History, Organization, and Assignments.

1. Sweden.

The Swedish Council on Medical Ethics was established by the parliament (the Riksdag) and given the status of National Council in March, 1984.

The national Council on Medical Ethics comprises seven *politicians* and eleven so-called *expert members* representing medical science, philosophy and the arts, law, the Catholic and Protestant churches and one member from the organizations of the disabled.

The Council's principal assignment is to maintain a continuous interchange of information and opinions concerning *research and medical treatment* of critical consequence to human integrity, or capable of influencing respect for human dignity. The Council is supposed to act as an *advisory* body to the Government and the Riksdag on questions of medical ethics. Its proceedings are to be made public and aim at encouraging debate, with particular emphasis on human equality and the right to physical and psychological integrity. The Council is also supposed to act as an intermediary between the scientific community, politicians, and the general public. However, there is no formalized cooperation between the National Council on Medical Ethics and the system of Regional Ethics Review Committees.

2. Denmark.

The Central Scientific-Ethical Review Committee (C-SERC) established in 1978 functions as a body of *appeal* for the seven R-SERCs in Denmark. Annually, the committee reviews approximately 10 to 15 such appeals. The Central Committee also represents the system of SERCs in relation to political authorities and the public. The Committee is composed of chairmen and vice-chairmen from the R-SERCs. The head and the deputy-chairman of the Committee are appointed by the Danish Medical Research Council (MRC) and must be a researcher and lay person, respectively. The Central Committee, as well as the seven R-SERCs, have a *semi-official* status. *No specific legislation regulates the field at present.*

In November 1988, however, the Minister of Health established a committee to consider the need for legislation on certain areas of biomedical research involving human subjects. The Committee finished its work in 1989, proposing a *statutory two-tier system of ethics committees* very similar to the existing system. The committee's bill has not as yet been considered by the Danish Parliament (Folketinget).

A second *central* body in medical ethics, the Danish Council of Ethics, was established by law in 1987, for subject areas *not* covered by the C-SERC. The seventeen members of the Council are appointed by the Danish Parliamentary Committee (nine members) and the Minister of Health (eight members). "The members of the Council must have publicly documented credentials concerning ethical, cultural, and social questions and may not be members of the parliament or the municipal or county councils" (2, p.139). The Council's two main assignments are to *promote public debate* and to submit proposals for new *legislation* within the field of medical research and development. The control of medical research projects is to remain the responsibility of the C-SERC, but the two independent central bodies are supposed to work in cooperation. Different models of cooperation have been proposed, of which the following seems to be the most promising: "Both organizations are preserved as independent, autonomous councils, but with a joint secretariat. Both organizations' work is given legislative status by a change and an addition to the current law on the Council of Ethics" (2, p. 145).

3. Norway.

The Norwegian MRC's Committee for Medical Research Ethics was established in 1978, and has, since the formation of the Regional Ethics Review Committees, acted as a *coordinating* and *advisory* body

in medical research ethics. A *working committee,* consisting of one member from each REC and headed by the chair of the MRC's Ethics Committee, convene four times a year. There is one annual meeting for all the REC and MRC committees. In addition, the chairmen of the committees convene once a year.

Through the years the MRC Committee has published a number of recommendations and reports on topics in medical ethics: informed consent, research on children, *in vitro* fertilization and artificial insemination, ethical questions connected with the registration of genetic disorders, treatment of sensitive personal data, and research on fetuses.

In June 1989, the Norwegian Parliament (Stortinget) endorsed the recommendation of a 1988 White Paper from the Ministry of Education and Research for the establishment of national research ethics committees within the following three subject areas of research and development:

1. medicine in a broad sense ("health and life sciences");
2. normative academic disciplines, i.e, the social sciences and the humanities - including law and theology;
3. natural science/technology, including those parts of biotechnology and genetic engineering that do not fall under medicine.

In the national committees great importance is placed on securing representation from the fields of *ethics* and *law*, and all of them have lay members as well. The members of the committees are appointed by the Ministry of Education and Research on the *recommendation* of the National Research Councils. The secretariats of the national committees are administered by the National Research Councils. The directors of the secretariats are required to have *background training in ethics* and are expected to do their own *research in ethics* in addition to their administrative responsibilities. For the subject area of medicine, the Government has given the Norwegian MRC's Committee for Medical Research Ethics the status of a National Committee for Medical Research Ethics (NEM). The committee has 12 members: 3 physicians; 3 members trained in ethics; 2 lay members; and 4 from relevant disciplines, such as biotechnology, the social sciences, personal data registers, and law.

The secretariat of the committee is located in the Center for Medical Ethics (CME) in the Science Park of the University of Oslo. According to the mandate presented by the Ministry of Education and Research (16 May 1990), the main assignments of NEM are the following:

a) to keep itself *continually informed* of current and potential questions of research ethics in the field of medicine;
b) to be the *coordinating* and *advisory* body for the RECs;
c) to *inform* researchers, the administration, and the public of current and potential questions of research ethics in the field of medicine;
d) to submit *reports* on matters of principle relating to medical research ethics, and comment on specific matters of special significance relating to research ethics;
e) to report on its activities at an open meeting at least once a year; in whatever ways it finds suitable promote informed discussion in society of ethical questions relating to medical science and knowledge; and
f) to keep other national and international research ethics committees informed of its activities, and in cooperation with them seek to establish a platform of principles of research ethics that extends beyond the boundaries of their respective research subjects.

REFERENCES

1. Central Scientific-Ethical Committee of Denmark. *Report for 1988.* Forskningsdirektoratet; 1989.
2. The Danish Council of Ethics. *Second annual report for 1989.* The Danish Council of Ethics; 1990.