

## Background Materials for Spak (1989)

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- 1 Robertson DM, Foulds LM, Leversha L, *et al*. Isolation of inhibin from bovine follicular fluid. *Biochem Biophys Res Commun* 1985;126:220-6.
- 2 McLachlan RI, Healy DL, Robertson DM, Burger HG, de Kretser DM. The human placenta: a novel source of inhibin. *Biochem Biophys Res Commun* 1986;140:385-90.
- 3 McLachlan RI, Healy DL, Robertson DM, Burger HG, de Kretser DM. Circulating immunoreactive inhibin in the luteal phase and early gestation of women undergoing ovulation induction. *Fertil Steril* 1987;48:1001-5.
- 4 Petraglia F, Sawchenko P, Lim ATW, Rivier J, Vale W. Localisation, secretion and action of inhibin in human placenta. *Science* 1987;237:187-9.

- 5 Mayo KE, Cerelli GM, Spiess J, *et al*. Inhibin A-subunit cDNAs from porcine ovary and human placenta. *Proc Natl Acad Sci USA* 1986;83:5849-53.
- 6 McLachlan RI, Robertson DM, Healy DL, Burger HG, de Kretser DM. Circulating immunoreactive inhibin levels during the normal human menstrual cycle. *J Clin Endocrinol Metab* 1987;65:954-61.
- 7 Robertson DM, Tsonis CG, McLachlan RI, *et al*. Comparison of inhibin immunological and in vitro biological activities in human serum. *J Clin Endocrinol Metab* 1988;67:438-43.
- 8 Hobson BM. Further observations on the excretion of chorionic gonadotrophin by women with hydatidiform mole. *Br J Obstet Gynaecol* 1958;65:253-9.
- 9 van Leusden HA. HCG in pathologic pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1973;3:137-46.
- 10 DuBsheter B, Berkowitz RS, Goldstein DP, Cramer DW, Berstein MR. Metastatic gestational trophoblastic disease: experience at the New England Trophoblastic Disease Center, 1965 to 1985. *Obstet Gynecol* 1987;69:390-5.
- 11 Schlaerth JB, Morrow CP, Kletzky OA, Nalick RH, D'Ablaing GA. Prognostic characteristics of serum human chorionic gonadotrophin titer regression following molar pregnancy. *Obstet Gynecol* 1981;58:478-82.

(Accepted 24 April 1989)

## Tissue response of gastric mucosa after ingestion of fluoride

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Br Med J 1989;298:1686-7

Results of macroscopic and microscopic evaluations of gastric mucosa and presence of nausea at control endoscopy and endoscopy after ingestion of 20 mg fluoride

Case No	Macroscopic evaluation*				Microscopic evaluation†				Nausea
	Body of stomach		Antrum		Body of stomach		Antrum		
	Control	Fluoride‡	Control	Fluoride‡	Control	Fluoride‡	Control	Fluoride‡	
1	1	4	0	4	0	2	0	2	Present
2	0	4	0	2	0	2	0	2	
3	0	4	0	2	0	3	0	2	Present
4	0	4	0	0	0	2	0	2	
5	0	4	0	1	0	2	0	1	
6	0	4	0	3	0	1	0	2	Present
7	0	4	0	0	0	3	0	1	
8	0	3	0	0	0	1	0	0	
9	0	4	0	0	0	2	0	2	
10	0	4	2	0	0	1	0	2	
11	0	4	0	2	0	1	0	0	Present
12	0	4	0	0	0	1	0	1	

\*Arbitrary scale: 0=normal, 1=one petechia or erosion, 2=two to five, 3=six to 10, 4=>10.

†Arbitrary scale: 0=normal, 1=either change in surface epithelium with oedema and haemorrhage of stroma or damage to gastric pits, 2=damage to both surface epithelium and gastric pits, 3=as 2 combined with acute inflammatory cellular response.

‡=Significant difference between fluoride and control according to Wilcoxon's signed rank test, p<0.01.

nations were similar (p<0.01, Wilcoxon's signed rank test). Two biopsy specimens were taken from the antrum and two from the body of the stomach. The histopathological changes were assessed on an arbitrary scale from 0 to 3.

After taking fluoride all subjects had petechiae or erosions (graded 3 or 4) in the body of the stomach and six had changes (graded 1-4) in the antrum. No petechiae or erosions were recorded in the oesophagus or the duodenum. In four subjects a layer of clotted blood was found over a large part of the gastric mucosa. The table shows the results of the macroscopic and microscopic evaluations. Three components of the gastric mucosa were affected by fluoride: the surface epithelium, the gastric pits, and the superficial stroma. The damaged epithelial cells were smaller than undamaged ones, and the vacuoles containing mucus were reduced in size or had disappeared. The most severely damaged epithelium was disrupted or totally lost. The most characteristic changes in the gastric pits were irregular dilatation and flattening of the epithelial cells. There was also a noticeable loss of mucin.

### Comment

Our study showed that one ingestion of fluoride at a dose used to treat osteoporosis affects the gastric mucosa. We do not know, however, to what extent repeated doses affect the mucosa, which might adapt after a while, as occurs with regular treatment with aspirin.<sup>3</sup> Our findings confirm data from experiments on animals, which showed that fairly low concentrations of fluoride can damage the surface of the gastric mucosa.<sup>4</sup>

The low pH of gastric juice and the formation of hydrogen fluoride probably caused the mucosal injuries. The uncharged molecule can easily penetrate the lipid cell membranes, enter the cell, and dissociate to fluoride and hydrogen ions, which may have toxic effects on enzyme systems and cause structural damage.

Symptoms like nausea and vomiting are not unusual when fluoride is used to treat osteoporosis.<sup>2</sup> They also occur occasionally when high doses are used for dental prophylaxis.<sup>5</sup> In our study only four subjects developed nausea, which suggests that using nausea as the first sign of fluoride toxicity might not be valid as all our subjects showed mucosal damage.

Finally, our results are also clinically important in dentistry because as much as 30 mg fluoride may be swallowed by children after prophylactic treatment with fluoride gel (1.23% fluoride).<sup>5</sup> If the risk of subsequent gastric injury is as high as our results suggest the use of such large amounts of fluoride in children should be questioned.

Part of this study was supported by grants from the Swedish Medical Research Council (No 6002) and the

- 1 Mamelle N, Meunier PJ, Dusan R, *et al*. Risk-benefit ratio of sodium fluoride treatment in primary vertebral osteoporosis. *Lancet* 1988;ii:361-5.
- 2 Riggs BL, Hodgson SF, Hoffman DL, Kelly PJ, Johnson KA, Taves D. Treatment of primary osteoporosis with fluoride and calcium. Clinical tolerance and fracture occurrence. *JAMA* 1980;243:446-9.

- 3 Lanza FL. Endoscopic studies of gastric and duodenal injury after the use of ibuprofen, aspirin, and other nonsteroidal anti-inflammatory agents. *Am J Med* 1984;77:19-24.
- 4 Pashley DH, Allison NB, Easman RP, McKinney RV, Horner JA, Whitford GM. The effects of fluoride on the gastric mucosa of the rat. *J Oral Pathol* 1984;13:535-45.
- 5 LeComte EJ. Clinical application of topical fluoride products—risks, benefits and recommendations. *J Dent Res* 1987;66:1066-71.

(Accepted 1 March 1989)

## Parents' beliefs about vaccination: the continuing propagation of false contraindications

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*Br Med J* 1989;298:1687

Low immunisation rates in England remain a cause for concern. The introduction of the measles, mumps, and rubella vaccine has renewed optimism that the proposed target of 90% uptake of vaccination could be achieved by 1990,<sup>1</sup> but studies in the early 1980s suggested that this target is unrealistic. They showed that parents and health care professionals had a poor understanding of the diseases concerned and commonly believed in mythical contraindications to vaccination. Our study aimed to reassess the importance of these obstacles to vaccination.

### Subjects, methods, and results

The study was conducted at this hospital during six weeks from December 1986 to January 1987. Children aged between 3 months and 4 years who were admitted to the communicable diseases unit and two general paediatric wards were entered into the study. Their immunisation history was sought from one or both parents. If the child had not been fully vaccinated at the correct times the parents were asked their reasons for the failure or delay. If they had been advised against vaccination they were asked for the source of advice and the reasons given. We defined the advice given as appropriate or otherwise according to the Department of Health and Social Security's guidelines of 1984.

During the study period 184 children were admitted, of whom 173 (94%) entered the study. A history of immunisation against measles was taken for the

121 children over 16 months old. No differences were found in any of the study variables between the groups admitted to the communicable diseases unit and the paediatric wards. Uptake of immunisation (diphtheria, tetanus, and polio 89% (154/173); pertussis 64% (111/173); measles 64% (77/121)) was similar to national figures<sup>2</sup> and figures for Wandsworth Health Authority during 1982-6. Altogether 106 children were incompletely vaccinated, and 91 of these had missed vaccinations for inappropriate reasons: in more than a third (39) the reason was parental objection (13) or apathy (26), but two false contraindications—temporary intercurrent infection and a history of atopy—accounted for a further third. Inappropriate advice was equally likely to have come from general practitioners, health visitors, and health clinics.

### Comment

In the early 1980s several studies examined the reasons for the continuing failure to improve uptake of vaccination.<sup>3,5</sup> Like those studies, ours highlighted serious deficiencies on the part of health care professionals in explaining and promoting immunisation. Most of the parents (96%) reported that they had received advice from a health care professional before deciding about their child's vaccination, and in only 28% of cases was failure to vaccinate the child due to parental inertia. In the remainder it was due to inappropriate advice or parental conviction not refuted by health care professionals. These findings support those of Blair *et al*,<sup>5</sup> who concluded that previous consultation with a health care professional did not significantly correlate with a parent's decision on vaccination.

Improving vaccination uptake is important, but we found that many parents, and apparently some doctors and health visitors, still viewed immunisation as a potential hazard that should be avoided if some excuse could be found. Our most important finding was that of all the cases in which the child had missed vaccinations, 38% could be attributed to either temporary intercurrent infection or atopy. This almost equalled the proportion accounted for by parental apathy and objection (42%). If these two misunderstandings had been specifically targeted uptake of more than 80% might have been achieved.

Much hope is being invested in the new measles, mumps, and rubella vaccine, but the obstacles to full vaccination highlighted in our study clearly reflect deeply entrenched attitudes. A more directed and sustained effort will be needed to change these if we are to improve uptake of vaccination.

Reasons given by parents for failure to immunise their children. Figures in parentheses are numbers of parents citing true contraindications according to Department of Health and Social Security's guidelines of 1984

	Pertussis	Measles	Diphtheria, tetanus, and polio	Total
Intercurrent illness:				
Febrile	4 (1)	5	1 (1)	18 (2)
Non-febrile	4	3	1	
Allergy:				
To egg	1	2 (2)		17 (2)
Atopy	7	5	2	
Convulsions:				
In child	(3)	2		8 (5)
In first degree relative	(2)	1		
In second degree relative	4	1		
Prematurity:				
Handicap	(3)	1		5 (3)
No handicap	3		1	
Natural infection	1	3		4
Previous reaction to vaccine	(2)			(2)
Immunosuppression		(1)		(1)
Apathy and objections	8	18	13	39
<b>Total</b>	<b>32 (11)</b>	<b>41 (3)</b>	<b>18 (1)</b>	<b>91 (15)</b>

1 Begg NT, Noah ND. Immunisation targets in Europe and Britain. *Br Med J* 1985;291:1370.



2 Central Statistical Office. *Social trends 18*. London: HMSO, 1988:123.

3 Nicoll A. Contraindications to whooping cough immunisation—myths or realities. *Lancet* 1985;i:679-81.

4 Campbell AGM. Measles immunisation: why have we failed? *Arch Dis Child* 1983;58:3-5.

5 Blair S, Shave N, McKay J. Measles matters, but do parents know? *Br Med J* 1985;290:623-4.

(Accepted 9 March 1989)

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:** Acute oral toxicity 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:** Spak, C-J., S. Sjostedt, L. Eleborg et al. (1989) Tissue response of gastric mucosa after ingestion of fluoride. Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden British Medical Journal 298:1686-7.

**SPONSOR:** N/A

**EXECUTIVE SUMMARY:**

In an acute toxicity study in humans (MRID 49489101), 12 healthy volunteers (4 males and 8 females), ages 22-45 years, were given a single 20 ml solution of sodium fluoride (containing 20 mg of fluoride). The subjects were given two endoscopies; one at least two weeks prior to dosing as a control and one two hours after ingestion of the sodium fluoride solution. The subjects fasted overnight prior to each endoscopy. During the endoscopy, macroscopic evaluations of the stomach and antrum were made. In addition, two biopsy samples were taken from each region for further histopathological analysis. The endoscopy was recorded and evaluated by a second gastroenterologist for confirmation.

Following sodium fluoride exposure, petechiae and erosions (grade 3-4) of the stomach were observed in all individuals and petechiae and erosions (grade 1-4) of the antrum were observed in 6 out of 12 individuals during endoscopy. In contrast, minimal findings were reported during the control endoscopies; one individual had a grade 1 lesion in the stomach and another individual had a grade 2 lesion in the antrum. Biopsy samples from the control endoscopy were all normal. However, following sodium fluoride ingestion, lesions were found in the stomach (grade 1-3) of all individuals and in the antrum (grade 1-2) of 10 out of 12 individuals. In addition, 4 of the 12 individuals reported nausea following ingestion of sodium fluoride.

A NOAEL was not identified in this study since effects were seen at the only dose tested. **The LOAEL is 20 mg F/dose (1000 mg F/L), based on nausea and lesions of the stomach and antrum.**

This acute oral toxicity study in humans is acceptable/non-guideline.

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

**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:** Not reported.**3. Subjects:**

**Sex:** 4 male, 8 female  
**Age:** 22-45 years

**B. STUDY DESIGN:****1. In life dates:** Not reported.**2. Subject assignment:** All individuals were given a 20 ml solution of sodium fluoride which contained a total of 20 mg fluoride (53 mmol/L).**C. METHODS:**

**1. Endoscopy:** Endoscopies for all patients were performed at least two weeks prior to dosing as a control. A second endoscopy was performed two hours after the subject were given a 20 ml solution of sodium fluoride containing a total of 20 mg fluoride. During the endoscopy the mucosa was graded according to an arbitrary scale (0 = normal, 1 = one petechia or erosion, 2 = two to five, 3 = 6 to 10, and 4 = >10). The stomach was also videotaped and the tape was later examined by another gastroenterologist. The results of both examinations were similar. Two biopsy specimens were taken from the antrum and two from the body of the stomach. Histopathological changes were assessed on an arbitrary scale from 0 to 3 (0 = normal, 1 = change in surface epithelium with edema and hemorrhage of the stroma or damage to gastric pits, 2 = damage to both surface epithelium and gastric pits, and 3 = same as grade 2 with an acute inflammatory cellular response).

**2. Statistics:** Differences in the results of the control endoscopy and the endoscopy following fluoride exposure, differences in the results of the histopathological analysis of the biopsies from the control endoscopy and the endoscopy following fluoride exposure, and differences between the first and second gastroenterologists grading of the mucosa following endoscopy were evaluated according to Wilcoxon's signed rank test,  $p < 0.01$ .

**II. RESULTS:**

- 1. Macroscopic:** During the control endoscopy, one individual had a finding of grade 1 in the body of the stomach and one individual had a finding of grade 2 in the antrum. After taking fluoride all subjects had erosions and petechiae (grade 3-4) in the body of the stomach. Six of these subjects also presented with findings in the antrum (grade 1-4). In addition, a layer of clotted blood was found over a large part of the gastric mucosa in 4 individuals. The results determined by the second gastroenterologist watching the videotape were similar (Wilcoxon's signed rank test,  $P < 0.01$ ). The findings in the stomach and antrum following exposure to fluoride were considered significantly different from the controls (Wilcoxon's signed rank test,  $P < 0.01$ ).
- 2. Microscopic:** Microscopic evaluation of the biopsies taken during the control endoscopy did not result in any abnormal findings. Microscopic evaluation of the biopsies taken during the endoscopy following fluoride exposure revealed findings on the body of the stomach in all individuals (grade 1-3) and on the antrum (grade 1-2) in 10 of the 12 individuals. The frequency of findings in the stomach and antrum following exposure to fluoride was considered significantly different from the controls (Wilcoxon's signed rank test,  $P < 0.01$ ).
- 3. Clinical Signs:** Nausea was reported by 4 individuals following exposure to fluoride.

**Table 1. Results of macroscopic and microscopic evaluation of gastric mucosa at control endoscopy and endoscopy after ingestion of 20 mg fluoride.**

Individual	Macroscopic <sup>1</sup>				Microscopic <sup>2</sup>			
	Stomach		Antrum		Stomach		Antrum	
	Control	20 mg Fluoride*	Control	20 mg Fluoride*	Control	20 mg Fluoride*	Control	20 mg Fluoride*
1 <sup>3</sup>	1	4	0	4	0	2	0	2
2	0	4	0	2	0	2	0	2
3 <sup>3</sup>	0	4	0	2	0	3	0	2
4	0	4	0	0	0	2	0	2
5	0	4	0	1	0	2	0	1
6 <sup>3</sup>	0	4	0	3	0	1	0	2
7	0	4	0	0	0	3	0	1
8	0	3	0	0	0	1	0	0
9	0	4	0	0	0	2	0	2
10	0	4	2	0	0	1	0	2
11 <sup>3</sup>	0	4	0	2	0	1	0	0
12	0	4	0	0	0	1	0	1

<sup>1</sup> 0 = normal, 1 = 1 petechia or erosion, 2 = 2-5 petechia or erosions, 3 = 6-10 petechia or erosions, 4 = >10 petechia or erosions

<sup>2</sup> 0 = normal, 1 = change in surface epithelium with edema and hemorrhage of stroma or damage to gastric pits, 2 = damage to both surface epithelium and gastric pits, 3 = as in 2 but with acute inflammatory cellular response.

<sup>3</sup> Reported nausea following fluoride exposure

\* Significantly different from the control, Wilcoxon's signed rank test,  $p < 0.01$ .

### III. DISCUSSION AND CONCLUSIONS:

**A. INVESTIGATORS' CONCLUSIONS:** The investigators concluded that one ingestion of fluoride resulted in effects on the gastric mucosa. The findings confirm data from animal experiments that indicate that fairly low concentrations of fluoride can damage the surface of the gastric mucosa.

**B. REVIEWER COMMENTS:** The reviewer agrees with the investigators conclusions. The gastric mucosa was adversely affected following a single ingestion of 20 mg fluoride. As only one dose was tested, a NOAEL was not established. The LOAEL was identified as 20 mg of fluoride per dose (1000 mg F/L).

**C. STUDY DEFICIENCIES:** The study only used one dose which limits the usefulness for determining a dose-response relationship. The number of individuals in the study was relatively small. The information reported in the study was limited; for example no information on purity or the vehicle used was reported. These deficiencies are relatively minor and do not change the overall conclusion of the study that a single dose of sodium fluoride causes adverse effects on the gastric mucosa.





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:** Spak, C.J. et al. (1989) Tissue Response of Gastric Mucosa after Ingestion of Fluoride. Karolinska Institute, Huddinge University Hospital, Huddinge, Sweden. *British Medical Journal*. 298:1686-7. (MRID 49489101)

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 FFDCFA.

**Summary Characteristics of the Research**

In this study, 12 subjects aged 22-45 years (8 females, 4 males) underwent two endoscopies after overnight fasts. One endoscopy was a control and the other was given after subjects ingested a single dose of 20 milliliters of sodium fluoride solution (containing 20 mg of fluoride). During the endoscopies, macroscopic evaluations of the stomach and antrum were performed, and two biopsy samples were taken from each region for further histopathological analysis. The control and post-exposure results were compared.

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

The objective of this study was to investigate the response of the gastric mucosa after a single dose of fluoride. The study was conducted at Huddinge University Hospital in Huddinge, Sweden in the 1980s. The results were published in *the British Medical Journal*

in June 1989. The study was partially funded by grants from the Swedish Medical Research Council and the National Institute of Dental Research/National Institutes of Health. 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 sulfur dioxide fluoride.

**2. Subject Selection:**

- a. **Demographics.** Twelve subjects aged 22-45 years (8 females, 4 males) participated in the study.
- b. **Pregnancy and Nursing Status.** There is no information about the pregnancy or nursing status of the female subjects.
- c. **Recruitment.** There is no information about how the subjects were recruited, but they are referred to as “volunteers” in the article.

**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 dose level in the study (20 mg fluoride) was less than 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 were no benefits to the subjects.
- c. **Risk-Benefit Balance.** There is no information about the risk-benefit balance. The researchers likely considered the potential societal benefits of increased understanding of fluoride effects to have outweighed the risks associated with the study because the dose level (20 mg) was considered safe at the time. The article notes that the dose was less than the amount of fluoride potentially swallowed by children (30 mg) following common prophylactic dental treatment with fluoride gel.

**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.

**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’ identities 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 because 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 mid-1980s by professors in the school of dentistry. Given the use of fluoride to prevent dental caries and some reports of gastric disturbances associated with fluoride treatment, the researchers were investigating the response of the gastric mucosa to fluoride.

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 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 adults, and there is no evidence that any of the eight female subjects 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.

First, I attempted to locate records from NIH and HHS because the article notes that the research was partially funded by a United States Public Health Services Grant. The NIH database contains records of grants issued as far back as 1989, and the HHS database contains grant records back to 1995. Since this study was published in 1989, it was funded prior to 1989, so it is not surprising that I was unable to locate any records of this study. I also attempted to obtain information about this study from the Swedish Medical Research Council, the Karolinska Institute, and the Regional Ethics Review Board for Karolinska. But to date I have received no responses to my email inquiries. Lastly, I also contacted the institutional review board at the University of Iowa, College of Dentistry, because one of the authors on the paper was affiliated with the college. They had no records of this research.

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 49489101 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.

**Appendix 1:**

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

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

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### 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.