Associated Pharmacologists & Toxicologists

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June 20, 1983

Dr. A. H. Hayes
Commissioner of Food & Drugs
c/o Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Citizens Petition that the FDA approval of the contraceptivs sponge be withdrawn

Enclosed are four copies of a Citizens Petition regarding the safety testing of the Polyurethane Foam Contraceptive Sponge.

Please file the petition and assign it a docket number. Also, please forward a copy of the petition to Dr. A. H. Hayes, the Commissioner of Food & Drugs, as soon as possible.

Sincerely yours,

Armand Lione, Ph.D.

Enc.

5510 - 16th Street, N.W. Washington, D.C. 20011 (202) 882-3811

DEPARTMENT OF HEALTH AND HUMAN SERVICES

June 21, 1983

Armand Lione, Ph.D.
President
Associated Pharmacologists &
Toxicologists
5510-16th St., N.W.
Washington, D.C. 20011

Dear Dr. Lione:

Your citizen petition request to refrain from approval the sale of polyurethane contraceptive sponge, dated June 20, 1983, was received by this office on June 20, 1983 and was assigned docket number 83P-0187/CP0002 and filed on June 21, 1983. Please refer to this docket number in future correspondence on this subject with the Agency.

This acknowledgement letter does not constitute approval or denial of, or other response, to your petition.

Sincerely,

Doris G. Brook
Dockets Management Branch

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE

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Associated
Pharmacologists &
Toxicologists

June 20, 1983

Dr. Arthur Hull Hayes
Commissioner of Food & Drugs
5600 Fishers Lane
Rockville, MD 20857

CITIZEN PETITION

The undersigned submits this petition under 21 CFR 1, 10.25 of the Federal Food, Drug and Cosmetic Act to request that you, Dr. Hayes, the Commissioner of Food and Drugs, withdraw FDA approval for the marketing of the Polyurethane Foam Contraceptive Sponge until such time that the manufacturers demonstrate that adequate premarketing safety testing, consistant with the recommendations of the FDA Panel on Vaginal Contraceptives, has been completed and evaluated.

STATEMENT OF GROUNDS

A. Summary

1. The spermicide used in the contraceptive sponge contains a demonstrated carcinogen, dioxane.
2. The dose of the spermicide, Nonoxynol - 9 (N-9), used in the contraceptive sponge has not been reviewed or approved by the FDA Section on Contraceptive Drugs.

(contd)

A. Summary - Statement of Grounds

3. The vaginal toxicity of polyurethanes and Nonoxynol - 9 for animals has been reported but the vaginal toxicity of the contraceptive sponge has not been studied in animals.

4. The absorption and accumulation of Nonoxynol - 9 has been demonstrated in animal experiments using radioactive tracers, but similar animal experiments have not been done to evaluate how the regular use of the contraceptive sponge may cause the accumulation of N-9 in human tissues.

5. Tests to determine the breakdown products of Nonoxynol - 9 in the contraceptive sponge when it remains at body temperature for two days have not been completed or evaluated.

6. The polyurethane used in the contraceptive sponge has not been submitted to intravaginal animal studies to evaluate its biodegradation, toxicity to the vaginal wall or its potential carcinogenicity.

7. The contraceptive sponge may increase the incidence of Toxic Shock Syndrome.

8. A plan for the postmarketing surveillance for harmful side effects of the contraceptive sponge has not been devised.

Detailed Statement of Grounds

1. The spermicide used in the contraceptive sponge, Nonoxynol - 9, contains a demonstrated carcinogen, dioxane. Dixoane is a contaminant of N-9 which forms during the synthesis of the spermicide. FDA chemists are aware of the presence of dioxane in N-9 and in the related food chemicals, the polysorbates (Food Chemical Codex, 1981). The methods for measuring the dioxane in polysorbate 60 and 80 were first reported by the FDA chemists, T.J. Birkel, C.R. Warner, and T. Fazio in 1979 (Birkel et al., 1979). Their report reviews the carcinogenicity of dioxane as follows:

> "Several researchers have reported on the carcinogenic activity of dioxane (Argus et al., 1965; Hoch-Ligeti & Argus, 1970; Hoch-Ligeti et al., 1970; Kociba et al., 1974; Argus et al., 1973). A review of published data by the International Agency for Research on Cancer (1976) led to their conclusion that '1,4-Dioxane is carcinogenic in rats and guinea-pigs by oral administration...'. In addition, the National Cancer Institute has recently reported (1978) that 1,4-dioxane is carcinogenic in rats and mice when administered in drinking water."

Since the report by Birkel et al. (1979) was published, a maximum tolerance limit for the dioxane in the polysorbates has been established at 10 ppm (Food Chemical Codex, 1981). In the development of the contraceptive sponge the 10 ppm dioxane maximum used for the polysorbate food chemicals has been arbitrarily applied to the chemically similar, Nonoxynol - 9.

The chronic toxicity or carcinogenicity of dioxane when administered intravaginally has not been investigated in the premarketing testing of the contraceptive sponge.

2. As currently formulated, each contraceptive sponge will contain one gram of Nonoxynol - 9. This dose of spermicide is larger than that used in any other contraceptive product. The safety of this unprecedented dose of Nonoxynol - 9 for use in a non-prescription contraceptive was not investigated or approved by the FDA Section on Contraceptive Drugs.

3. There are recent reports in the scientific literature of animal studies which evaluate the vaginal toxicity of polyurethanes (International Agency for Research on Cancer, 1979; Chvapil et al., 1979) and Nonoxynol-9 (Chvapil et al, 1980). The review paper by Dr. B. Vorhauer (Vorhauer, 1980) on the premarketing testing of the contraceptive sponge does not describe any intravaginal animal studies that were done with this product. The intravaginal testing of the contraceptive sponge was not described in the October, 1982 presentation given by the manufacturers of the contraceptive sponge, VLI Corporation, to the Fertility and Maternal Health Drugs Advisory Committee (1982). Dr. E. Connell, former Chairman of the FDA Panel on Review of Contraceptive s and Other Vaginal Drug Products, reported the Panel's recommendations in 1979. The vaginal application of new vaginal contraceptives, in rabbits, is among the toxicity tests required by Dr. Connell's Panel to evaluate product safety (see Table below, from: Connell, 1979). Dr. Connell is now a scientific advisor for the VLI Corporation.

TABLE 22-5. Vaginal Contraceptives: Animal Toxicity Studies

TYPE OF TEST	ANIMAL SPECIES	TESTING REQUIRED
Acute	Rat or mouse	LD_{50}
Subacute and/or chronic	Non-rodent	12 mo of exposure
	Rodent	24 mo of exposure
Local	Rabbit	Vaginal application
	Guinea pig	Intradermal or cutaneous

4. The absorption and accumulation of Nonoxynol - 9 has been demonstrated in animal experiments using radioactive tracers (Chvapil et al., 1980). These studies demonstrated that N-9 is readily absorbable from the vagina into the blood stream. Measurable quantities of radioactivity could be found in the urine of test animals six days after a single intravaginal dose of N-9. The radioactive tracer from N-9 was also found in the milk of test animals that were lactating. Animal experiments using radioactive tracers have not been done to monitor the absorption of N-9 from the contraceptive sponge.

5. When used in the contraceptive sponge, one gram of Nonoxynol - 9 will be placed in the vagina and remain at body temperature for at least 48 hours. Tests to determine the chemical stability of N-9 at elevated temperatures are currently underway. The results of the tests may be reported by July 1, 1983. If the contraceptive sponge is allowed to be sold beginning on July 1, 1983, this product will be available for human use before the results of these tests can be compiled or evaluated.

6. A substantial number of reports are available on the biodegradation of polyurethanes when in chronic contact with animal and human tissues (reviewed in: Slade & Peterson, 1982), as well as the acute toxicity of polyurethanes to the vaginal tissues of rabbits and rats (Chvapil et al., 1979) and the induction of cervical and ovarian tumors by intravaginal polyurethane (International Agency for Research on Cancer, 1979). A sizable literature also suggests that some polyurethanes can cause tumor formation when implanted in human tissues (Autian et al., 1975; Hueper, 1964).

6. (contd) A summary of the preceding data on the intravaginal toxicity and carcinogenicity of polyurethanes was recently transmitted to Dr. Soloman Sobel, Head of the FDA Division on New Drugs, who supervised the FDA safety review of the contraceptive sponge. (copy enclosed)

In light of the existing literature on the vaginal toxicity of polyurethanes and the absence of intravaginal animal tests with this product, despite the recommendations of the FDA Panel on Vaginal Contraceptives (Connell, 1979), the premarketing safety testing of the contraceptive sponge appears to be grossly inadequate.

7. The contraceptive sponge may increase the incidence of Toxic Shock Syndrome. In testimony before the Fertility and Maternal Health Drugs Advisory Committee on October 28, 1982, Dr. Hoi Leung, a FDA statistician, said, " The first issue is whether the use of the sponge during menstruation will increase the risk of contracting toxic shock syndrome, and my answer to this question is that based on the results of the study, we don't really know, because the number of women in the study was small..."

Later in the same presentation, Dr. B. Vorhauer, President of the company marketing the contraceptive sponge, referred to test results which showed that the Nonoxynol-9 on the contraceptive sponge could kill bacteria that were innoculated into a clean sponge, if the sponge was allowed to sit in a clean beaker for varying amounts of time. These results are not clearly relevant to concerns about toxic shock syndrome. They do not demonstrate that N-9 can keep bacteria from growing in a sponge that has been worn for two days and absorbed menstrual blood.

8. Recently, Stolley et al. (1979) described an epidemiological system for the post-marketing surveillance of adverse effects of vaginal contraceptives. Based on comments made by members of Dr. Sobel's group on June 8, 1983, there are no plans to have a post-marketing surveillance system in place when the contraceptive sponge is scheduled to be marketed on July 1, 1983.

Conclusion

The preceding statement of grounds summarizes the existing literature on the toxic effects of polyurethanes, Nonoxynol - 9 and the carcinogenic N-9 contaminant, dioxane. The intravaginal tests that are necessary to evaluate the safety of the contraceptive sponge have been described in a previous report by a FDA Panel (Connell, 1979). Until these studies are completed and evaluated, a judgement that the contraceptive sponge is safe enough for sale as a non-prescription contraceptive would seem to be ill-founded.

In light of the available information on the presence of a carcinogen in Nonoxynol - 9 and the existing reports of acute and chronic damage that polyurethanes and N-9 can cause when administered intravaginally to test animals, this petition requests that the FDA withdraw approval for the marketing of the Polyurethane Foam Contraceptive Sponge until these safety questions can be addressed in detail.

(See below for a list of Scientific Reference Articles & Certification)

Scientific Reference Articles

Argus, M.F., Arcos, J.C., & Hoch-Ligeti, C. (1965) Studies on the Carcinogenic Activity of protein denaturing agents: hepatocarcinogenicity of dioxane. J. Natl. Cancer Inst. 35, 949-958.

Argus, M.F., Sohal, R.S., Bryant, G.M., Hoch-Ligeti, C & Arcos, J.C. (1973) Dose-Response and Ultrastructural Alterations in Dioxane Carcinogenesis. Eur. J. Cancer 9, 237-243.

Autian, J., Sing, A.R., Turner, J.E., Hung, G.W.C., Nunez, L.J. & Lawrence, W.H., (1975) Carcinogenesis from polyurethanes," Cancer Resch, 35, 1591-6.

Birkel, T.J., Warner, C.R., Fazio, T. (1979) Gas Chromatographic Determination of 1,4-Dioxane in Polysorbate 60 and Polysorbate 80. J. Assoc. Off. Anal. Chem. 62, 4, 931-5.

Chvapil, M.,Chvapil, T.A., Owen, J.A., Kantor, M., Ulreich, J.B. & Eskelson, C. (1979) Reaction of Vaginal Tissue of Rabbits to Inserted Sponges Made of Various Materials, J.Biomedical Mat. Resch. 13, 1-13.

Chvapil, M., Eskelson, C.D., Stiffel, V., Owen, J.A., Droegemueller, W. (1980) Studies on Nonoxynol-9. II. Intravaginal absorption, distribution, metabolism and excretion in rats and rabbits. Contraception, 22, 3, 325-339.

Connell, E.B., (1979) Vaginal contraception: current FDA status, p. 221-233, in: Vaginal Contraception: new developments, ed. by G.I. Zatuchni, A.J. Sobrero, J.J. Speidel, J.J. Sciarra, Harper & Row, Hagerstown 389 p.

Fertility and Maternal Health Drugs Advisory Committee. (1983) Meeting Transcript. October 28, 1982, afternoon session, p. 145-232. FDA, Hearing Clerk, Rockville, MD.

Food Chemical Codex (1981) 3rd ed. National Academy of Science, p. 234-6, 477.

Hoch-Ligeti, C., & Argus, M.F. (1970) Induction of Carcinomas in the nasal cavity of rats by dioxane. Br. J. Cancer 24, 164-7.

Hoch-Ligeti, C., Argus, M.F. (1970) At. Energy Symp. Ser. 21, 267-9.

Hueper, W.C. (1964) Cancer Induction by Polyurethan and Polysilicone Plastics. J. Natl. Cancer Inst., 33, 6, 1005-1022.

International Agency for Research on Cancer, "Evaluation of the carcinogenic risk of chemicals to humans: some monomers, plastics and synthetic elastomers, and acrolein," 19, 326-331, World Health Organization (1979)

Reference Articles (contd)

Kociba, R.J., McCollister, S.B., Park, C. Torkelson, T.R., & Gehring, P.J. (1974) 1,4-Dioxane. I. Results of a two year ingestion study in rats. Toxicol. Appl. Pharmacol. 30, 275-286.

National Cancer Institute (1978) Carcinogenesis Technical Report Series No. 80, Bethesda, MD.

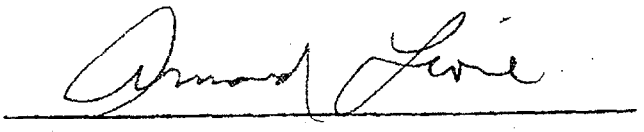
Slade, C.L. & Peterson, H.D., "Disappearance of the polyurethane cover of the Ashley Natural Y Prosthesis," Plast. Reconstruc. Surg. 70 (3) 379-83 (1982)

Stolley, P.D., Davies, J.L., Shapiro, S., Slone, D., (1979) Components of an epidemiologic system for the surveillance of adverse effects due to vaginal contraceptives, p. 271-276 in: Vaginal Contraception: new developments, ed. by G.I. Zatuchni, A.J. Sobrero, J.J. Speidel, J.J. Sciarra, Harper & Row, Hagerstown, 389 p.

Vorhauer, B.W. (1980) Human reporduction: bioengineering aspects of contraception applied to the development of a new female contraceptive, p. 93- in: Biofluid Mechanics - 2, ed. by D.J. Schneck, Plenum, N.Y. & London, 519 p.

Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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