

Robert J. Staab Ph.D.
President

(201)934-6203 res.
(201)327-0035 ph/fx

RTA

Regulatory and Technical Associates
73 Franklin Tpk. Allendale, NJ 07401

Fax Header Sheet

Date: 2/10/06

Company: Ansell

To: Mr. Lon McIlvain

Fax # 334-615-2574,

From: R.J. Staab

pages including this one: 5

Dear Mr. McIlvain:

You have asked that I review the new FDA- proposed label for condoms. Much of the label contains verbiage, which accurately depicts the effectiveness of condoms, and standardizes wording for the packages. I do have some concerns about the labeling that has been proposed for nonoxynol-9 condoms as well as the table comparing barrier contraceptives.

The FDA has been pushing for comparative charts for all forms of contraceptives for years. Recently, CDER adjusted the table when the Today Sponge was approved. There are obvious errors in the table as it is based on Dr. Trussel's chart which was published in the non-peer reviewed text Contraceptive Technology by Dr. Hatcher. Having said that, there will always be errors in any chart devised since there is not a single well controlled comparative study of all methods of birth control. The supposed advantage of the chart, especially for OTC products is a simple consumer friendly method for comparison. In my opinion, the proposed table does not meet that objective.

Nonoxynol-9 is one the ingredients reviewed by the FDA's Panel for Contraceptive and Other Vaginal Drug Products. Following evaluation of all of the available laboratory and clinical data, the Panel concluded (Federal Register/Vol 45, No. 241/Friday, December 12, 1980/Proposed Rules, pp. 82028-82031) "that Nonoxynol 9 (a nonionic surfactant) is safe and effective for OTC use as a vaginal contraceptive as specified in the dosage section of the report". It also stated "the directions for use should be clearly stated and illustrated in order to provide easily understandable guidance to the consumer.

There are numerous nonoxynol-9 containing OTC products, which continue to be classified by the FDA as safe. During a Nonprescription Drug Advisory Panel meeting, Dr. Betty Connel reported that Nonoxynol 9 has been shown to produce vaginal irritation in about 1-4 percent of users; a similar incidence of sensitivity has been observed in sexual partners. About 8 percent of users have complained of vaginal itching, soreness or dryness. It has been suggested that damage to the vaginal mucosa might increase the risk of STD transmission but this has not been clinically documented with statistical validity.

I believe that this is still the case. The suggestions that have come from the current literature confirm that nonoxynol-9 at some doses can produce irritation, yet they do not confirm irritation to the degree that it has broken down the barrier capacity of the vagina or skin into which it comes in contact. The basic arguments of dose/response hold in that as we decrease the dose (exposure) we should scientifically expect a decrease in the response.

Dr. Connel has reported that one study has measured the frequency of genital ulcers and vulvitis following use of the nonoxynol-9 containing sponge by sex professionals in Africa. She has pointed out that the sex workers had a higher prevalence of genital ulcers than the placebo group prior to the initiation of the study. During the study the sex workers used multiple sponges per day. It was concluded that no reduction in HIV infection was found in the Sponge users who averaged 40 to 50 partners per week. Dr. Connel reported that "Clearly, this study cannot be used to compare to consumer use where frequency is expected to be about three times per week." She also pointed out that the sponge contains 1 gram of N-9, but releases approximately 125-150 mg in 24 hours. This is 10-20 percent of the total amount.

The panel listened to her opinion and agreed to recommend the approval of this OTC product for sale as a safe and effective product on the US market. The US FDA has recently reviewed the safety of this sponge product containing one gram nonoxynol-9 and concluded that it is safe and effective for daily use.

In an original report, COL-1492 a nonoxynol-9 (N-9)-containing vaginal gel showed some potential as a microbicide. As part of the effectiveness trial, an initial toxicity study was conducted. The main objective of the reported study was the assessment of the toxicity of a 52.5 mg N-9 gel, COL-1492, when used a number of times each day by female sex workers. This was a randomized, placebo-controlled triple-blinded trial among female sex workers. The participants were asked to use the product for each vaginal sexual act. At each monthly visit a gynecological examination with sexually transmitted disease sampling and colposcopy was performed. Venous blood was drawn for syphilis and HIV serology. All women received intensive counseling on condom use. Male condoms and sexually transmitted disease treatment were given free of charge. Only blinded results on the colposcopic examinations are reported. The incidence of lesions with or without an epithelial disruption was low: 0.06 and 0.29, respectively, per 100 woman-days in group A; 0.09 and 0.26 respectively per 100 woman-days in group B. There was no significant difference between the two arms. The authors concluded that multiple daily use of COL-1492 by female sex workers did not show an increase of local toxicity over that of a placebo. Colposcopy was discontinued in the autumn of 1997 in accordance with a Data Safety Monitoring Board decision. In the currently ongoing effectiveness trial the assessment of the product's toxicity continues to be monitored by simple visual examination.¹

¹ Safety of multiple daily applications of COL-1492, a nonoxynol-9 vaginal gel, among female sex workers. COL-1492 Phase II Study Group

More recent studies have shown, however, that nonoxynol-9 does not provide protection against sexually transmitted infections (STIs), and that in some cases, it may actually increase the risk of transmission by irritating the epithelium of the vagina and anus.²

A randomized study of women sex workers found a slightly higher risk of gonorrhea, a slightly lower risk of chlamydia, and no change in risk for HIV among women using film with 70 mg of nonoxynol-9.³

A subsequent study of women with high STI risk who were not sex workers compared nonoxynol-9 gel and condom use against condom use alone for the prevention of gonorrhea and chlamydia. The women who used the gel had a 20 percent higher incidence of gonorrhea, chlamydia, or both, than women who only used condoms. Women had a 50 percent greater chance of acquiring gonorrhea if they used the gel than women who did not, but gel users had a comparable probability of acquiring chlamydia.⁴

One highly publicized randomized, four-year study involving nearly 1,000 sex workers found that the use of a gel with 52.5 mg of nonoxynol-9 increased risk of HIV infection by 50 percent. The women in this study reported very high rates of sexual activity, averaging 75 sexual encounters per month. The women who used the gel most frequently, some women used it up to 20 times a day, were at the greatest risk of HIV infection.⁵ One study evaluated the effectiveness of the vaginally administered spermicide nonoxynol-9 (N-9) among women for the prevention of HIV and other sexually transmitted infections (STIs). A systematic review of randomized controlled trials was conducted. Nine such trials including 5096 women, predominantly sex workers, comparing N-9 with placebo or no treatment, were included. Primary outcomes were new HIV infection, new episodes of various STIs, and genital lesions. Five trials included HIV and nine included STI outcomes, and all but one (2% of the data) contributed to the meta-analysis. Overall, relative risks of HIV infection (1-12, 95% confidence interval 0.88-1.42), gonorrhoea (0-91, 0-67-1-24), chlamydia (0-88, 0-77-1-01), cervical infection (1-01, 0-84-1-22), trichomoniasis (0.84, 0-69-1-02), bacterial vaginosis (0-88, 0-74-1-04) and candidiasis (0-97, 0-84-1-12) were not significantly different in the N-9 and placebo or no treatment groups. Genital lesions were more common in the N-9 group (1-18, 1-02-1-36). Our review has found no statistically significant reduction in risk of HIV and STIs, and the confidence intervals indicate that any protection that may exist is likely to be very small.

Van Damme, L; Chandeying, V; Ramjee, G; Rees, H; Sirivongrangson, P; Laga, M; PerrieAns, J AIDS
Volume 14 number 1 2000 Jan 7PP85-8

² WHO/CONRAD — World Health Organization. (2002, accessed July 12). "WHO/CONRAD Technical Consultation on Nonoxynol-9".

³ Roddy, R., et al. (1998). "A Controlled Trial of Nonoxynol-9 Film to Reduce Male-to-Female Transmission of Sexually Transmitted Diseases." *New England Journal of Medicine*, 339(8), 504-10.

⁴ Roddy, R., et al. (2002). "Effect of Nonoxynol-9 Gel on Urogenital Gonorrhea and Chlamydial Infection: A Randomized Controlled Trial." *JAMA*, 287(9), 1117-22.

⁵ Van Damme, L. (2000). "Advances in Topical Microbicides" Presented at the XIII International AIDS Conference, July 9-14, 2000, Durban, South Africa.

There is some evidence of harm through genital lesions. N-9 cannot be recommended for HIV and STI prevention.⁶

The CDC's recommendation is that "N-9 should not be recommended as an effective means of HIV protection". It can be more harmful than protective. Condoms with N-9 in the lubricant have a much lower level than that found to be harmful at this time. However, it is critical that the opinion of the CDC is that a condom lubricated with N-9 is clearly better than using no condom at all. The protection provided by the condom against HIV far outweighs the potential risk of N-9. If given the option, condoms without N-9 may be a better option for HIV prevention." Nonoxynol-9 is still recommended by CDC for use as a spermicide.⁷ This advice remains sound.

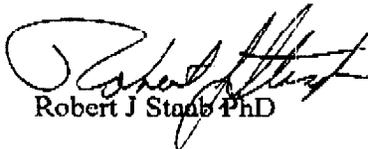
Overall, the more recent studies appear to confirm that multiple daily exposures to nonoxynol 9 at high doses can disrupt vaginal and rectal membranes. There are no data that can be used to conclude that STD transmission occurs when low doses of nonoxynol 9 are used.

Ansell spermicidal condoms are coated with the lubricant which is 8% N-9 in propylene glycol. So, for a typical dose of 400 mg of lubricant, there would be 32 mg of N-9 in the condom package. A portion of this remains in the foil package. As well a portion is on the inside of the condom (penis contact side) and a portion is on the outside (vaginal contact side). Although exact lubricant measurement on the vaginal side is not available, it is reasonable to conclude that no more than 10 mg nonoxynol 9 is available to either partner. This 10 mg would be in a lubricant base at e.g. 8% concentration in propylene glycol. These doses approach de minimus levels when compared to the 50 to 150 mg doses that have been studied. Certainly, these doses do not approach the exposures that sex workers might become exposed to when they have multiple daily partners.

⁶ Nonoxynol-9 spermicide for prevention of vaginally acquired HIV and other sexually transmitted infections: Systematic review and meta-analysis of randomised controlled trials including more than 5000 women
Wilkinson, D.; Tholandi, M.; Ramjee, G.; Rutherford, G. W.
Lancet Infectious Diseases 2/10 (613-617) 01 OCT 2002

⁷ Helene D. Gayle, M.D., M.P.H. Centers for Disease Control and Prevention
August 4, 2000

The warnings currently being suggested by the Agency would have a negative impact on the use of condoms by giving the false impression that condom use is hazardous. The conclusion of the CDC and FDA CDER in recent actions appear to be reasonable in that the benefits to users of nonoxynol 9 outweigh the risks and it is reasonable to continue to encourage condom use; with or without these low levels of nonoxynol 9.



Robert J Staab PhD

DABT, RAC