



Memorandum

Date June 6, 1985

From QRAC (Quantitative Risk Assessment Committee)

Subject Asbestos in Talc

To W. Gary Flamm, Ph.D.
Director, Office of Toxicological Sciences (HFF-100)

Using Linda Taylor's report [1] and other information on asbestos and talc, we conclude that the added human risk of lung cancer and mesothelioma from possible asbestos in talc is less than 10^{-8} lifetime risk and quite possibly orders of magnitude less. We have used, as our population at risk, infants that may be routinely dusted with talcum powder for an estimated period of 2 years.

Infant Dose and Worker Exposure:

Based upon one experimental 2 yr. exposure scenario for talcum powder dusting, babies would apparently inhale no more than about 6.5×10^3 asbestiform fibers per year (4.95 talc fibers/cc $\times 1000$ cc/l $\times .58$ l/min. breathing rate $\times 43.8$ min/wk powdering $\times 52$ wk/yr. $\times .1\%$ asbestos in talc). The asbestiform fibers are difficult to detect, poorly defined in shape, and of a highly variable subtype. We assume .1% tremolite or anthophyllite asbestos in talc based on 1977 FDA measurements and other recent samples [1, 10, 11]. To be called asbestiform fibers, the fibrous silicates must be greater than 5 μ m. and have length/width ratio greater than 3. These inherent detection and geometrical measurement limitations for asbestos in talc make comparisons with worker exposure to a different type (mainly amosite, crocidolite and chrysotile) and shape of asbestos highly problematical [5]. In fact there is a

general consensus that current talc mines are virtually free of asbestos (offending mines have gradually been abandoned) and that any residual silicates in talc are so finely and smoothly ground as to represent virtually no risk to humans whatsoever even where an occasional fiber just barely satisfies the technical definition for asbestiform fibers. However, this consensus belief would require better geometric measurements than currently exist for both current commercial talc fibers and for workplace asbestos fibers during the past 50 years. Nevertheless, baby exposure in fibers per year is crudely estimated at about 0.3×10^{-6} times that of worker exposure in several well known epidemiological studies (e.g., Selikoff study: $15 \text{ f/ml in workplace} \times 12,000 \text{ ml/min breathing rate} \times 60 \text{ min/hr} \times 8 \text{ hr/day} \times 5 \text{ days/wk} \times 50 \text{ wks./yr.} = 2.16 \times 10^{10} \text{ f/yr.}$ vs $6.5 \times 10^3 \text{ f/yr for baby}$) [1].

A complicating factor, however, is that human cancer risk from these studies seems to follow different time-dose response patterns for the two main cancer endpoints (lung cancer and mesothelioma). Although several human epidemiological studies exist which could be utilized for quantitative risk assessment purposes, it is most illustrative to consider the largest of these occupational studies, namely, that of Selikoff, et. al. [7,8] in which 17,800 insulation workers were exposed to a mixed variety of asbestos fibers (mainly amosite and chrysotile) for about 25 years on average. Through 1976, 2,271 deaths (12.7% of total) had occurred.

Lung Cancer:

Lung cancer rates were about 4.6 times average (486 observed/106 expected). Since this nearly 360% excess lung tumor

rate seems to apply to nonsmokers alone as well as smokers and nonsmokers combined [6], then, assuming hypothetically that one can extend excess relative risks to very low asbestos exposures, one would expect to see an excess lifetime lung tumor rate among asbestos exposed nonsmokers of about 1.8% (360% x the normal lifetime nonsmoker lung tumor rate of about .5% - integrating 1979 survival rates against Garfinkel's 1960-1972 nonsmoker age-specific lung tumor rates [12, 13]). Excess lung cancer rates appear to be proportional to dose and duration of exposure, but not to some high power of time-since-first-asbestos exposure [6]. Thus, excess lifetime lung cancer risk for talc exposed babies who will never smoke would appear to be approximately the product of 1) an excess 1.8% lifetime risk for nonsmoking asbestos exposed workers, 2) a baby/worker yearly exposure ratio of 0.3×10^{-6} , and 3) a baby/worker exposure duration ratio of 2 yrs/25 yrs. This product yields a value of $.4 \times 10^{-9}$ added lifetime risk for lung tumors. Similarly, averaging eventual smokers in with the lifelong nonsmokers assumed above, the average added lifetime lung cancer risk for the talc exposed baby will be at worst about 10 times higher or about $.4 \times 10^{-8}$. We note that current (1979) lifetime total respiratory cancer rates are about 5% and have nearly doubled since 1960, possibly reflecting rapidly changing smoking patterns during and after World War II, primarily among women. However, decreased tar levels in cigarettes and decreased per capita use of cigarettes since about 1965 should result in a gradual leveling off or decline in the total respiratory and/or lung cancer rate of the general population [14].

Mesothelioma:

The estimation of lifetime risk of mesothelioma is somewhat more difficult since the mesothelioma response data appears quite nonlinear in time since first exposure. We have investigated four different methods of mathematically modelling the nonlinear mesothelioma data. They all indicate an upper bound on lifetime risk for talc powdered infants of about 10^{-8} risk and quite possibly a much lower upper bound if the conservative assumptions upon which they were based do not hold. These four methods consisted of mathematically treating mesothelioma as 1) a nonincidental tumor with no time lag between tumor initiation and death, 2) a nonincidental tumor with a 10 year time lag between tumor initiation and clinical observation, 3) an incidental tumor, and 4) treating asbestos as a first stage intervener in an Armitage-Doll multistage carcinogenic process [9].

In fact methods 1-3 yielded virtually identical risks ($.5-.75 \times 10^{-8}$ risk). While method 4 yielded a risk 2-3 times higher (1.5×10^{-8} risk), it could easily have yielded a risk up to several orders of magnitude lower than 10^{-8} if we had simply assumed asbestos intervenes at a later stage of the carcinogenic process in this hypothetical Armitage-Doll multistage model. There was general concurrence among these four methods, and it suffices to briefly summarize Method 1. Method 1: based upon fitting $bt^{3.1}$ (nonincidental analysis) to a 1922-1946 cohort of the Selikoff, et. al. data.

A reasonably simple way to estimate the median life (ML) risk to median survival age 77 (in 1979) for humans exposed 2 yrs. to talcum

powder during infancy is given by the product of the following terms:

- (a) (77 yrs. since first exposure for infants/37 yrs. since first exposure for 1922-46 cohort as of 1978⁺)^{3.1} = 9.70.
- (b) (2 yr. infant exposure duration/34 yrs. approx. worker exposure duration for 1922-1946 worker cohort) = .059.
- (c) (infant/worker) yearly exposure ratio = 0.3×10^{-6} .
- (d) 1922-1946 cohort cumulative mesothelioma response of 3.75% (180 mesotheliomas/4,800 cohort members).

This product yields a median life risk of $R_{ML} = 0.64 \times 10^{-8}$.

Tumors other than Lung and Mesothelioma: (Selikoff study)

Although significant tumor increases were observed at other sites in the workers (e.g., esophagus, stomach and colon), their risk is dominated by that of the lung (less than 10^{-9} or 10^{-8} risk, depending upon whether or not the baby becomes a smoker) and by mesothelioma risk (less than 10^{-8} risk).

Other Comments on Total Cancer Risk:

These estimates of added lifetime human cancer risk are 2 orders of magnitude below those implied in Linda Taylor's memo 1) due to the fact that the more recent detection studies suggest .1% or less asbestos in talc on average rather than the 1% assumed by Dr. Taylor: and 2) due to a 10 fold conversion error going from fibers/cc in the air to fibers inhaled/yr by the infant.

Although mothers may receive an exposure for each infant powdered, their added lifetime risk from talc should be relatively smaller than the infant's since their mouths and noses are considerably further from the densest portion of the talc cloud than is the case for the captive infant during the daily powdering period (the inverse square law for exposure may apply).

Finally, the risks implied by the Selikoff study are generally on the high side of those implied by the other smaller epidemiological studies and we see little value in repeating calculations here for those studies (see reference 6 for details).

Ovarian Talc Study:

For completeness, a discussion is presented on a human epidemiological study purporting to show an association between talc use (talcum powder used for genital dusting on the perineum or on sanitary napkins) and ovarian cancer.

The Cramer et.al. study [2], which purported to show a significantly increased relative risk for ovarian cancer associated with talc use, 1) appears to have been misinterpreted statistically, 2) was uncorrected for several likely biasing factors and 3) appears to have been strongly contradicted by another study showing a reduced relative risk as significant in the negative direction as the Cramer study was in the positive direction.

The Cramer study's most prominent analysis (Mantel-Haenszel) was adjusted for only 2 factors and gave a relative risk (RR) of around 1.92 (p less than .003) and 95% confidence limits of 1.27 to 2.89 for 215 cases (talc users for genital or sanitary napkin dusting) vs 215 controls. Cramer's more comprehensively adjusted but seemingly de-emphasized multivariate regression analysis for 9 possible simultaneously confounding variables yielded a smaller and much less significant relative risk of 1.61 (p=.03), with 95% confidence limits of 1.04-2.49. It should be noted that the crude relative risk with no adjustments whatsoever was 1.89. In any case, if the authors had limited their logistic regression analysis as they subsequently did for their Mantel-Haenszel analysis, to those 121 cases where the first chosen control did not refuse to participate

(refusal bias), then the resulting p-value can be predicted through extrapolation of the other reported analyses to be greater than .05 and perhaps greater than .1. Unfortunately, the authors did not report this analysis. Instead they selectively chose to point out only that the relative risk of those exposed to talc both as a genital dusting powder and through sanitary napkins declined from a relative risk of 3.28 (p less than .001) to 2.44 (p less than .05) when the potentially biasing control refusals were eliminated from analysis. Apparently the authors felt it unnecessary to report those p-values that were greater than .05.

Since there were twice as many singles among the cases (21%) as among the controls (11%), the life style of singles might easily have biased the original overall relative risk of 1.92 [3]. However, the multivariate logistic analysis (RR=1.61) using all of the original 215 cases and 215 controls clearly adjusted for marital status along with such variables as religion, educational level, ponderal index, age at menarche, exact parity, oral contraceptive or menopausal hormone use, and smoking. The partially adjusted Mantel-Haenszel analysis (RR=1.92) only adjusted for menopausal status and crude parity.

Furthermore, it is generally assumed that any real positive cancer effect will show an increased risk with increased dose. Cramer only reported one subanalysis where he crudely considered dose response. He divided the small group of talc-dusted diaphragm users into those using diaphragms less than 5 years and into those using diaphragms more than five years. However, rather than showing an increased relative risk with increased dose (increased length of usage), the relative risk actually decreased noticeably

though not in a "statistically significant" fashion from 1.82 to 1.23 as diaphragm use increased from less than 5 years to more than 5 years.

In addition to the above interpretations of Cramer's own results, several potentially biasing factors could not be adjusted for by the logistic analysis. First, a possible positive correlation between talc use and ovarian disease etiology due to patient-perceived hygienic or cosmetic reasons would bias the relative risk upwards [4]. Second, a recall bias among hospital cases relative to community controls is quite plausible since cases may have greater incentive as well as opportunity to recall whether they should classify themselves as talc users [3]. Talc users from the community may well be modest in either participating as controls (the refusal bias already discussed) or in subsequently admitting talc use as a control subject. The recall bias might be expected to be even greater - as was possibly observed - for estimation of the relative risk for those using talc both on sanitary napkins and as a dusting powder ($RR=3.28$, p less than .001; or $RR=2.44$, p less than 0.05, after the refusal bias is eliminated) than for those engaged in only a single type of use.

Finally a talc and ovarian cancer study by Hartge, et. al. [4], appears to strongly contradict the reportedly positive Cramer study. Overall 135 cases and 171 control women matched by age, race and hospital were questioned on talc use. The estimated relative risk of ovarian cancer by talc users was reported to be 0.7 (95% confidence interval of 0.4 to 1.1). Adjustments for race, age, and gravidity (pregnancy) had no effect upon the estimate. No subanalyses

resulted in relative risks significantly greater than 1. It would appear that no refusal bias was operative in the Hartge study since none was reported. Also it would appear that recall bias was non-existent since there appeared to be no recall bias on the use or nonuse of douching.

SUMMARY

In summary, any hypothetical systemic added lifetime cancer risk (e.g., mesothelioma and lung cancer) to humans due to asbestos fibers in talc (principally for babies subject to 2 years of talc dusting) appears to be less than 10^{-8} added lifetime risk and possibly several orders of magnitude lower risk still, depending upon assumptions and uncertainties alluded to above, especially those regarding geometrical shape of any possible asbestos fibers in talc, and limits of detection for asbestos in talc. In addition, there appears to be no association between customary human talc use per se and ovarian cancer.

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ATTACHMENT:

Signature Page

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