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 $R_{ML} = 0.64 \times 10^{-8}$.

Method 2: based upon $b(t-10)^{2.1}$ (delayed observation or time lagged nonincidental analysis).

Note that to estimate real mesothelioma incidence (time of mesothelioma induction - the last stage of the multistage cancer process) at age x, the worker must be assumed to have been autopsied or surgically inspected at some average age, say x+10. Thus, assumming the worker stops exposure 3 years before death, the component relative and absolute risk factors for incidence at age 77 now are the following:

(a) ((87 yrs.-10 yrs.)/(37 yrs.-10 yrs.)$^{2.1}$ = 9.03.

(b) (2 yr. infant exposure duration/(37-10) yr. worker exposure duration) = .074.

(c) (infant/worker) exposure rate ratio = 0.3×10^{-6}.

(d) 3.75% mesothelioma response in 1922-1946 cohort

Thus $R_{ML} = 0.75 \times 10^{-8}$.

Method 3: based upon $bt^{1.64}$ (prevalence or incidental analysis):

The relative and absolute risk product factors are:

(a) (77 yrs. since first exposure for infant/35 yrs. since first exposure for the 2,271 deaths to 1976)$^{1.64}$ = 3.64.

(b) (2 yr. infant exposure/34 yr. ave. worker exposure duration for 2,271 deaths to 1976) = .059.

(c) (infant/worker) exposure rate ratio = 0.3×10^{-6}.

(d) 7.7% mesothelioma cumulative prevalence to 1976 (175 mesotheliomas/2,271 deaths).

Thus $R_{ML} = 0.50 \times 10^{-8}$.

Method 4: based upon $bt^{3.1}$ (nonincidental analysis) and a first stage effect in a generalized multistage process.

We assume that bt^{k-1} fits the time-response data of a nonincidental tumor and is consistent with a first-stage-only effect in a generalized multistage process (with K stages), where biological time t starts at age of first exposure and continues until death [9]. Although this is not precisely true for the 1922-46 asbestos worker cohort, it appears to be approximately true. Moreover the time lag from cessation of exposure to end of followup (1976 or 1978^{+}) is assumed to be small compared to total duration of exposure (i.e., exposure duration is a large fraction of time since first exposure). However, the exposure duration for infants is very small compared to median lifespan. Thus, while we fit worker yearly incidence data to bt^{k-1} we should extrapolate yearly incidence (I) for exposed infants using the expression $I = b(t^{K-1} - (t-d)^{K-1})$ for a K stage multistage process with duration of exposure d and time since first exposure t [9].

Now K-1 = 3.1 from Fig. 1 and b can be written as the product of a constant K_m and f where f is the time adjusted yearly dose of asbestos fibers in ml-yrs. K_m is a constant dependent upon the type and dimensions of the asbestos. Since f = 3.43 f/ml-yr. (15 ave. f/ml in workplace (1922-1946) x 8 hrs./24 hrs. x 5 days/7 days x 50 wks/52 wks) for the Selikoff study, K_m can be computed from the plot of $I = K_m f\, t^{3.1}$ in Fig. 1. At t = 20 yrs, $I = 5.6 \times 10^{-4}$, implying that the $\ln K_m = \ln(5.6 \times 10^{-4}) - \ln(3.43) - 3.1(\ln 20) = -7.49 - 1.23 - 9.29 = -18.01$.

Thus $K_m = 1.51 \times 10^{-8}$ (same as Peto obtains). Continuing, $I = K_m f(t^{K-1} - (t-d)^{K-1}) = K_m f t^{K-1}(1-(1-d/t)^{K-1})$ which roughly = $K_m f t^{K-1}(d/t)(K-1)$ for d much less than t (using Taylor expansions). Thus yearly incidence is approximately $I = K_m fd(K-1)t^{K-2}$. Integrating (without correcting for decreasing survival) over a total of T years yields a cumulative incidence of about $I_c = K_m fdT^{K-1}$. If d = 2 yrs. infant exposure duration, T = 77 yrs., K-1 = 3.1, f = 3.43 f/ml-yr. for worker x 0.3×10^{-6} (infant/worker exposure ratio) = 1.03×10^{-6} f/ml-yr., and $K_m = 1.51 \times 10^{-8}$, then $I_c = 2.2 \times 10^{-8}$.

However, this figure assumes no mortality from competing causes of death and does not even adjust for the effect of previous mesothelioma related deaths. Factoring in a standard population age-specific mortality or corresponding survival function into the above integral would yield a median life risk of about 75% of 2.2×10^{-8} or $R_{ML} = 1.6 \times 10^{-8}$. This correction for survival can vary depending upon the limits of integration and what functional forms are under the integral, but for median life risk estimates the correction ranges from 1.0 down to .5 at worst. We also note that integrating I out to 100 yrs. of life with

respect to a standard mortality curve should yield approximately the same risk as cumulative incidence to median age 77 yrs. without any mortality adjustments. These approximately cancelling effects of two mathematical refinements may support the utility of using the median lifespan in simple calculations.

Comments on the 4 Mesothelioma extrapolation methods:

First and most importantly, it should be noted that the first 3 methods yield virtually identical median lifespan risks for babies exposed to talc for 2 years ($.5-.75 \times 10^{-8}$). Thus many of the debates over the "correct model" appear somewhat superfluous. In particular heated debates over whether mesothelioma rates follow given high or low powers of time appear to be superfluous since the power of time is compensatingly related to other poorly defined and difficult to measure conceptual model parameters (e.g., tumor stage initiation and consequent time lag to clinical detection or death, and context of tumor observation (incidental or nonincidental)). Furthermore, small perturbations of the rough estimates of worker exposure or the power of time (K) have only a small effect on the overall risk.

All the above models appear to be reasonable summary descriptors of the observable data and result in simple extrapolatory tools for the given problem of inferring median lifetime risk from infant exposure. One can always make method 4 computationally more difficult if one avoids use of the approximations.

A second observation is that the rough mutual agreement of the results of the 4 extrapolation methods does not necessarily imply that

the obtained excess median life risk is accurate even if the infant and worker exposure were to the same type and dimension of asbestos fiber. For example, none of the four models take into account the possibility that accumulated dose rather than yearly dose rate might more accurately reflect the biological burden of asbestos due, for example, to its ability to reside in vivo in the lung, pleural or peritoneal lining for years without being excreted (although encystment may be possible). Note also that we did not define dose on a mg/kg body weight basis. Although, we prefer such a definition for routine compounds that are ingested and metabolized, we strongly suspect that routine approach to be inappropriate for asbestos. In addition, all 4 methods assume linearity in response vs. dose at all dose levels. However, we have virtually no reliable dose response data from any of the epidemiological studies.

Furthermore, some investigators have suggested that the nonconstant accumulated asbestos dose may be as conceptually consistent with a late stage multistage carcinogenic process as the more usually defined yearly asbestos dose rate appears to be consistent with a first stage Armitage-Doll multistage process [9]. Although the theory and computations are more complicated for nonconstant exposures, it does appear that median life risks from infant exposure to asbestos affecting only a late stage in the carcinogenic process will generally result in much smaller risks than those calculated above for a first-stage-only effect in the carcinogenic process.

Our third observation which we have just hinted at is that method 4 above (the first-stage-only effect in a multistage model) may be just another way of implementing method 1, but just slightly more computationally difficult and having a slightly higher risk, partially because it substitutes a theoretical risk integration against the current (1979) U.S. population's standard survival function for the implicitly observable but poorer asbestos worker's cumulative survival of an earlier era in a more toxic environment. For example, the method 4 risk is about 2.6 times greater than the average risk of methods 1-3. There are probably other reasons for this 2.6 fold increase in risk over methods 1-3. However, since even partial intervention of asbestos fibers at later stages of the carcinogenic process in the Armitage-Doll multistage model imply lower overall risks, we prefer the simpler methods 1-3 at this moment to the more complicated multistage models whose proper application with respect to the stage or stages affected is still very much in doubt.

In general, we do not put a lot of faith in mechanical use of sophisticated but unverifiable models, but we will occasionally refer to them as in method 4 where we can suggest implicit and perhaps elucidative connections to apparently more humble and simpler procedures.

Summary:

All four mathematical methods of modelling the nonlinear mesothelioma response data from the Selikoff study indicate a lifetime added human risk to infants exposed 2 years to talc powdering of at most about 10^{-8} risk, and quite probably far less risk, if for example, asbestos intervenes in the carcinogenic process at a later stage than the first stage which was assumed in method 4 for the Armitage-Doll multistage process.

Robert N. Brown

Robert N. Brown

REFERENCES

1. L. Taylor, "Request for CAC Evaluation of the Hazard of Asbestos Contamination of Cosmetic Talc," FDA memo, Nov. 15, 1984.

2. D.W. Cramer, MD, W.R. Welch, R.E. Scully, C.A. Wojciechowski, "Ovarian Cancer and Talc - A Case Control Study," Cancer, July 15, 1982.

3. L. Tollefson, "Review of reports of increased risk of ovarian cancer from talc use," FDA memo, Jan. 30, 1985.

4. P. Hartge, R. Hoover, L. Lesher, L. McGowan, "Talc and Ovarian Cancer," JAMA, Oct. 14, 1983.

5. L. Tollefson and F. Cordle, "Review of an assessment concerning asbestos contamination of cosmetic talc," FDA memo, Dec. 17, 1984.

6. Chronic Hazard Advisory Panel on Asbestos, Report to the U.S. Consumer Product Safety Commission, July, 1983.

7. Selikoff, I.J., Hammond, E.C., Seidman, H., Mortality Experience of Insulation Workers in the United States and Canada, 1943-1976, Annals of the N.Y. Academy of Sciences, 1979, 91-116.

8. Peto, J., Seidman, H., Selikoff, I.J., Mesothelioma Mortality in Asbestos Workers: Implications for Models of Carcinogenesis and Risk Assessment, Br. Jour. of Cancer (1982) 45, 124-135.

9. Day, N.E., Brown, C.C., Multistage Models and Primary Prevention of Cancer, JNCI, 64, 977-989 (1980).

10. Eiermann, Heinz J., "Health Research Group Inquiry on Talc Safety," FDA memo, Aug. 28, 1978.

11. Wenninger, John A., "Denial of Petition for 'Labelling of Warning of the Hazardous Effects Produced by Asbestos in Cosmetics Talc' from Philippe Douillet," FDA memo, July 11, 1984.

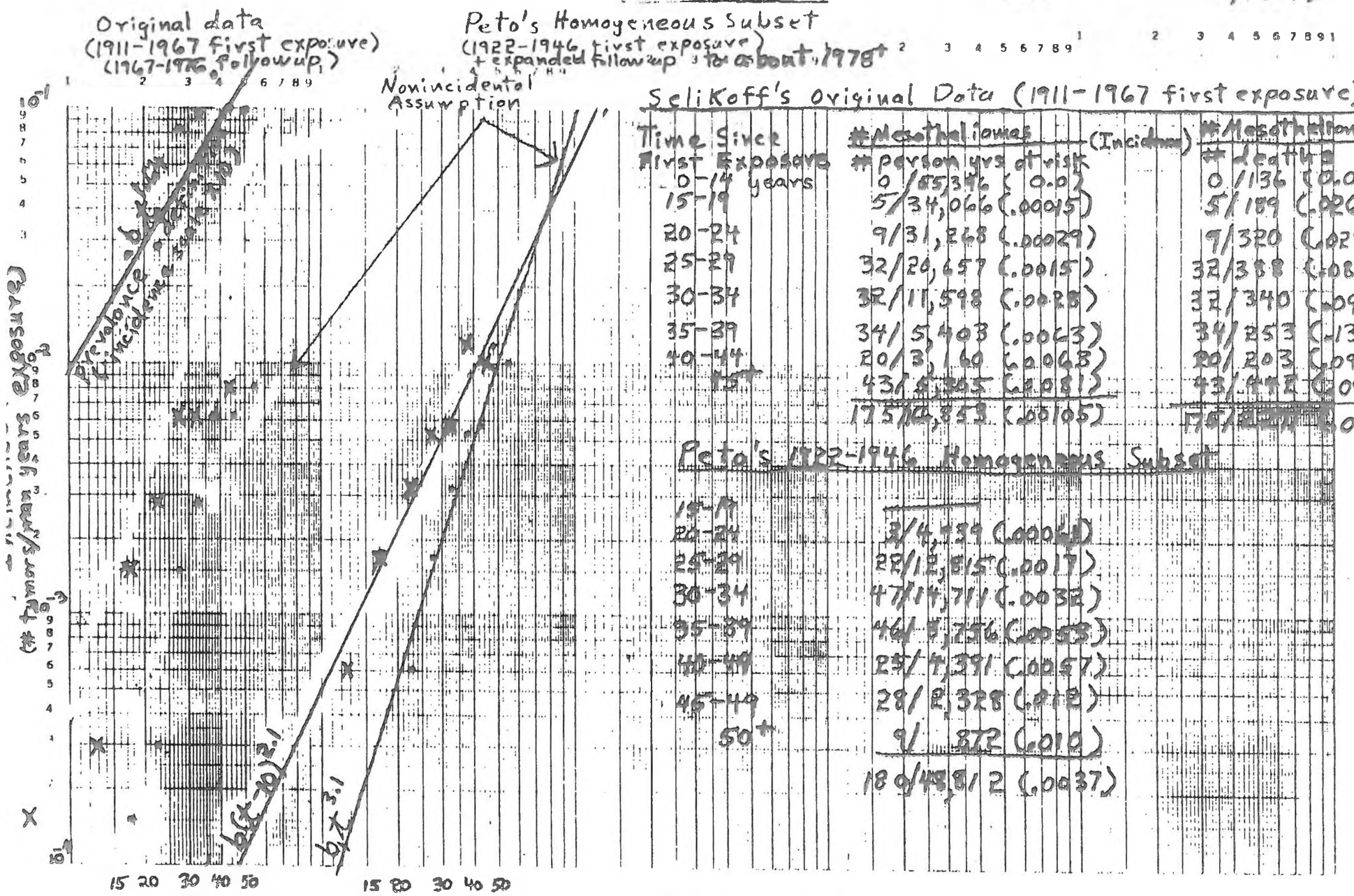
12. Garfinkel, L., "Time Trends in Lung Cancer Mortality Among Nonsmokers and a Note on Passive Smoking," JNCI, 66, 1061-1066.

13. Vital Statistics of the United States, Mortality, Part A, 1979, published by the U.S. Dept. of Health and Human Services.

14. U.S. Dept. of Health and Human Services, PHS, "The Health Consequences of Smoking: Cardiovascular Disease," a report of the Surgeon General, 1983.

Selikoff Asbestos Study (17,800 workers on asbestos union roles as of Jan. 1, 1967)

Mesotheliomas



• no time lag
X 10 yr. time lag

Selikoff's Original Data (1911-1967 first exposure)

Time Since First Exposure	# Mesotheliomas / # person yrs at risk (Incidence)	# Mesotheliomas / # Deaths
0-14 years	0 / 85,346 (0.0)	0 / 136 (0.0)
15-19	5 / 34,066 (.00015)	5 / 189 (.026)
20-24	9 / 31,248 (.00029)	9 / 320 (.028)
25-29	32 / 20,657 (.0015)	32 / 388 (.082)
30-34	32 / 11,598 (.0028)	32 / 340 (.094)
35-39	34 / 5,403 (.0063)	34 / 253 (.134)
40-44	20 / 3,160 (.0063)	20 / 203 (.098)
45+	43 / 5,345 (.0081)	43 / 444 (.097)
	175 / 165,853 (.00105)	175 / 2274 (.077)

Peto's 1922-1946 Homogeneous Subset

15-19	3 / 4,739 (.00063)
20-24	22 / 12,815 (.0017)
25-29	47 / 14,711 (.0032)
30-34	46 / 9,256 (.0050)
35-39	29 / 4,391 (.0066)
40-44	28 / 2,328 (.012)
45-49	9 / 872 (.010)
50+	
	184 / 48,812 (.0037)

JUL 11 1986

Phillippe Douillet
One Holyoke Lane
Stony Brook, New York 11790

Re: Docket No. 83P-0404

Dear Mr. Douillet:

This responds to your November 8, 1983, petition requesting that cosmetic talc be labeled with an asbestos warning statement, information on asbestos particle size, and the proportion of talc impurities in the product.

You assert that, because the mining of talc almost invariably includes the mining of asbestos as well, cosmetic talc may contain significant amounts of asbestos particles that present an inhalation hazard to humans. Also, you cite references to substantiate that significant amounts of asbestos have been found in commercial talc samples, that asbestos inhalation is hazardous to humans, and that asbestos contaminants in talc will produce toxicological responses when inhaled.

FDA recognizes that asbestos inhalation over extended periods is hazardous to humans. The agency is also aware that some cosmetic talc produced in the 1960s and early 1970s did contain asbestiform minerals. However, your petition has not persuaded us that the cosmetic talc that is presently being produced contains significant amounts of asbestiform minerals.

During the early 1970s, FDA became concerned about the possibility that cosmetic talc did contain significant amounts of this material. The agency received several reports about such contamination. However, at that time, the analytical procedures for determining asbestos in talc were not fully developed, and most of the analytical work was conducted without scientific agreement as to which methods were well-suited for the identification of asbestiform minerals in talc. Consequently, FDA considered all analytical results to be of questionable reliability. This assessment proved to be correct because many questions were subsequently raised about results reported in the literature in the early 1970s (see enclosed copy of National Bureau of Standards Special Publication 506 entitled "Misidentification of Asbestos in Talc"). Because of the questionable nature of the analytical results, the agency was not able to assess reliably the levels of asbestiform minerals in cosmetic talc then in the marketplace.

Under these circumstances, FDA decided that the most appropriate actions that it could take to protect the public health would be to make the reports public and to request assistance from the affected industry in developing acceptable analytical procedures. This approach apparently has led to considerable improvement in the quality of this talc.

After FDA took these actions, many cosmetic manufacturers began to analyze their talc for asbestiform minerals as part of their quality control programs, and talc suppliers began to sell higher purity talcs to the cosmetic industry. By 1976, asbestos analytical methodology was sufficiently developed that the Cosmetic, Toiletry, and Fragrance Association (CTFA) could issue a specification (copy enclosed) for cosmetic talc. This specification required that such talc be free of fibrous amphibole (e.g., asbestos in the form of asbestiform tremolite) using a CTFA method of analysis that is capable of detecting 0.5 percent of amphibole asbestos. This specification contributed to the continued improvement of cosmetic talc quality.

In addition, FDA surveillance activities that were conducted in the latter portion of the 1970s showed that the quality of cosmetic talc had significantly improved, and that even when asbestos was present, the levels were so low that no health hazard existed. Our scientists recently reviewed data from these surveillance activities and concluded that the risk from a worst-case estimate of exposure to asbestos from cosmetic talc would be less than the risk from environmental background levels of exposure to asbestos (non-occupational exposure) over a lifetime.

Consequently, we find that there is no basis at this time for the agency to conclude that there is a health hazard attributable to asbestos in cosmetic talc. Without evidence of such a hazard, the agency concludes that there is no need to require a warning label on cosmetic talc.

FDA should also point out that, in reviewing your petition, we found several problems with the information on which you relied. The publication "Asbestiform Impurities in Commercial Talcum Powders," which you cite in your petition, appears to contain a number of significant errors that lead us to question the accuracy of the findings that were reported. For your information, we have enclosed a copy of a June 8, 1973, rebuttal of this publication that was written by the Chief Mineralogist of the Colorado School of Mines Research Institute in Golden, Colorado. Also, your petition's 1978 book reference to the Mt. Sinai School of Medicine findings is too old to reflect present contamination levels. Further, we are not convinced that the Mt. Sinai findings pertained to cosmetic talc. Your reference states that common commercial talcs were analyzed, but it does not specify whether these commercial talcs were industrial grade or cosmetic talc.

For all of these reasons, your petition is denied. This denial is without prejudice to the future filing of a petition on this matter, accompanied by all relevant data in support of the petition.

Sincerely yours,

/s/ J. W. Swanson

Acting Associate Commissioner
for Regulatory Affairs

Enclosures

cc: HFC-1
HFC-200 (#G-86-182)
HFC-220 (Rogers/file)
HFF-1
HFF-100
HFF-152
HFF-300
HFF-302
HFF-310
HFF-440
GCF-1 (Horton/Derfler)
HFA-224
HFA-305

Prepared:JRTaylor:5/15/86
Initialled:JRTaylor:5/15/86, 6/5/86
EJCampbell:5/15/86, 6/5/86
HJEiermann:5/16/86, 6/9/86
JAWenninger:5/19/86
WGFlamm:5/29/86, 6/9/86
LRLake:5/29/86, 6/12/86
RJLenahan:5/29/86, 6/10/86
LBBrock:6/10/86
RWGill:6/12/86
F/T:JRTaylor:sag:6/4/86
Concurred:EBrisson:6/27/86
Retype:RLSpencer:cdk:6/27/86:disk.26 (#1.32)
Revised:PSDerfler:7/3/86
Retype:RLSpencer:cdk:7/7/86
Concurred:PDerfler:7/8/86
Revised:Concurred:LHorton:7:9/86
F/T:RLSpencer:bka:7/10/86

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Acting Director, Office of Compliance
Center for Food Safety and Applied Nutrition

Denial of Petition to Require Warning Statements on Cosmetic Talc

Associate Commissioner for Regulatory Affairs (HFC-1)
Through: Director, Center for Food Safety and Applied Nutrition

---

OBJECTIVE

To issue a letter of denial (Tab A) for a petition from Mr. Philippe Douillet that requests certain mandatory labeling on cosmetic talcs to warn consumers of asbestos hazards associated with such products.

FACTS

During the early 1970's FDA became concerned that significant amounts of asbestiform minerals may be present in cosmetic talc. The agency had received reports of cosmetic talc being contaminated with high levels of asbestiform minerals. However, at that time the analytical procedures for determining asbestos in talc were not fully developed and most of the analytical work was conducted without scientific agreement as to which methods were suited for the identification of asbestiform minerals in talc. FDA then considered all analytical results to be of questionable reliability. As a result, the agency could not assess either the accuracy of the reported results or the extent of the presence of asbestiform minerals in cosmetic talc then in the marketplace. FDA made the reports public and requested assistance from the affected industry in developing acceptable analytical procedures. Subsequently, many cosmetic manufacturers began to analyze talc for asbestiform minerals as part of their quality control programs and talc suppliers began to sell higher purity talcs to the cosmetics industry. By 1976 asbestos analytical methodology was sufficiently developed that the Cosmetic, Toiletry and Fragrance Association (CTFA) could issue a specification for cosmetic talc that required such talc to be free of fibrous amphibole (e.g., asbestos in the form of asbestiform tremolite) by a CTFA method of analysis which was capable of detecting 0.5% of amphibole asbestos. This specification contributed to the continued improvement of cosmetic talc quality.

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
HFE-362	J K Taylor	6/5/86	HFO	Douillet	06/09/86			
HFE-315	E Campbell	6/5/86	OTS	Clayton	6/9/86			
HFC-310	[illegible]	6/5/86						

FDA surveillance activities that were conducted in the latter portion of the 1970's showed that the quality of cosmetic talc had significantly improved, and that even when asbestos was present, the levels were so low that no health hazard existed. Our scientists recently reviewed data from these surveillance activities and concluded that the risk from a worst-case estimate from cosmetic exposure would be less than the risk from environmental background levels of asbestos (nonoccupational exposure) over a lifetime (Tab B).

On November 8, 1983, Mr. Philippe Douillet submitted a petition (Tab C-Docket No. 83P-0404) requesting that cosmetic talc be labeled with an asbestos warning statement and information on asbestos particle size and the proportion of talc impurities in the product. The petition contends that cosmetic talc is contaminated with asbestos and that this contamination presents an inhalation hazard. The petition's substantiation of this contention consisted only of twenty references. None of the references was recent enough to indicate that cosmetic talc contains any asbestiform minerals at this time.

DISCUSSION

Because Mr. Douillet's petition contains no substantiation of a health hazard attributable to asbestos in cosmetic talc at this time, we have drafted a letter of denial (Tab A) for your approval. The draft letter of denial explains why we do not believe asbestos contamination problems exist at this time. We did not include the recent scientific evaluation of asbestos risk as an enclosure for the draft letter but we plan to forward the evaluation to the Dockets Management Branch upon issuance of the letter of denial.

RECOMMENDATION

It is recommended that the draft letter of denial concerning asbestos warning statements on cosmetic talc be approved and issued.

L. Robert Lake

Attachments

Tab A - Draft Letter of Denial
Tab B - Scientific Evaluation of Asbestos Risk
Tab C - Philippe Douillet's November 8, 1983 Petition

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE

DECISION

The letter of denial of Philippe Douillet's petition concerning asbestos warning statements on cosmetic talc is:

Approved _____ Disapproved _____ Date _____

Prepared by:HFF-312:TAYLOR:485-0179

cc:
HFF-1
HFF-100
HFF-152
HFA-305
HFF-300 r/f
HFF-302
HFF-312
HFF-312 r/f
HFF-440
HFF-310 r/f
HFC-1 r/f
Draft:JRTaylor:sag:5/15/86
Initialled:JRTaylor:5/15/86
EJCampbell:5/15/86
HJElermann:5/16/86
JAWenninger:5/19/86
WGFlamm:5/29/86
LRLake:5/29/86
R.J. Lenahan:5/30/86
F/T:JRTaylor:sag:6/5/86

FILE
COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE

Phillippe Douillet
1 Holyoke Lane
Stony Brook, NY 11790

Dear Mr. Douillet:

This responds to your November 8, 1983 petition requesting that cosmetic talc be labeled with an asbestos warning statement, information on asbestos particle size, and the proportion of talc impurities in the product.

You assert that because the mining of talc almost invariably includes the mining of asbestos as well, cosmetic talc may contain significant amounts of asbestos particles that present an inhalation hazard to humans. Also, you cite references to substantiate that significant amounts of asbestos have been found in commercial talc samples, that asbestos inhalation is hazardous to humans, and that asbestos contaminants in talc will produce toxicological responses when inhaled.

FDA recognizes that asbestos inhalation over extended periods is hazardous to humans. Also, the agency is aware that some cosmetic talc produced in the 1960's and early 1970's did contain asbestiform minerals. However your petition has not persuaded us that more recently produced cosmetic talc contains any significant amounts of asbestiform minerals.

During the early 1970's FDA became concerned that significant amounts of asbestiform minerals may be present in cosmetic talc. The agency had received reports of cosmetic talc being contaminated with high levels of asbestiform minerals. However, at that time the analytical procedures for determining asbestos in talc were not fully developed and most of the analytical work was conducted without scientific agreement as to which methods were suited for the identification of asbestiform minerals in talc. FDA then considered all analytical results to be of questionable reliability. This assessment was later proved correct because many questions were subsequently raised about results reported in the literature (see enclosed copy of National Bureau of Standard Special Publication 506 entitled Misidentification of Asbestos in Talc). As a result, the agency could not assess either the accuracy of the reported results or the extent of the presence of asbestiform minerals in cosmetic talc then in the marketplace. Under these circumstances, FDA decided that the most appropriate course of action to protect the public health was to make the reports public and to request assistance from the affected industry in developing acceptable analytical procedures. This approach appeared to lead to considerable improvement in the quality of this talc. Many cosmetic manufacturers began to analyze talc for asbestiform minerals as part of their quality control programs and talc suppliers began to sell higher purity talcs to the cosmetic industry. By 1976 asbestos analytical methodology was sufficiently developed that the Cosmetic, Toiletry and Fragrance

Association (CTFA) could issue a specification (copy enclosed) for cosmetic talc that required such talc to be free of fibrous amphibole (e.g., asbestos in the form of asbestiform tremolite) by a CTFA method of analysis which was capable of detecting 0.5% of amphibole asbestos. This specification contributed to the continued improvement of cosmetic talc quality.

In addition, FDA surveillance activities that were conducted in the latter portion of the 1970's showed that the quality of cosmetic talc had significantly improved, and that even when asbestos was present, the levels were so low that no health hazard existed. Our scientists recently reviewed data from these surveillance activities and concluded that the risk from a worst-case estimate from cosmetic exposure would be less than the risk from environmental background levels of asbestos (nonoccupational exposure) over a lifetime.

Accordingly, we believe it would be inappropriate to consider implementing your requested labeling requirements for cosmetic talc without adequate substantiation of a health hazard attributable to asbestos in cosmetic talc at the present time. Your petition contains no such substantiation. The publication "Asbestiform Impurities In Commercial Talcum Powders" appears to contain a number of significant errors that lead us to question the accuracy of the findings that were reported. For your information, we have enclosed a copy of a June 8, 1973 rebuttal of this publication that was written by the Chief Minerologist of

the Colorado School of Mines Research Institute in Golden, Colorado. Also, your petition's 1978 book reference to the Mt. Sinai School of Medicine findings is too old to reflect present contamination levels. Further, we are not convinced that the Mt. Sinai findings pertained to cosmetic talc. Your reference states that common commercial talcs were analyzed, but it does not specify whether these commercial talcs were industrial grade or cosmetic talc.

In view of these facts, your petition is denied. This denial is without prejudice to the future filing of a petition in this matter, accompanied by all relevant data in support of the petition.

Sincerely yours,

Joseph P. Hile
Associate Commissioner for
Regulatory Affairs

cc:
HFF-1
HFF-100
HFF-152
HFA-305
HFF-300 r/f
HFF-440
HFF-310 r/f
HFC-1 r/f

Draft:JRTaylor:5/15/86
Initialled by:JRTaylor:5/15/86
EJCambell:5/15/86
HJEiermann:5/16/86
JAWenninger:5/19/86
WGFlamm:5/29/86
LRLake:5/29/86
RJLenahan:5/30/86
F/T:JRTaylor:sag:6/4/86

Hon. Mark Novitch
Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20460

Petition for labeling of warning
of the hazardous effects produced by
asbestos in cosmetic talc.

The purpose of this petition is to request a labeling of warning as well as a detailed list of components of the commercial cosmetic talcs. Because of its geological formation cosmetic talc may contain significant amounts of asbestos particles producing hazardous effects by its continuous use. Since it is a cosmetic article its production and commercialization is regulated by the Food, Drug and Cosmetic Act. I am a graduate student of Marine Environmental Sciences and I am deeply concerned by the toxic effects produced by the constant and periodic use of talc by the public, specially children.

Because commercial talc deposits consist of natural admixtures of mineral, a number of mineralogically different materials have been used as commercial talc. Asbestos is a generic term for a variety of natural minerals which have the ability to be separated in filaments (1 Since the mining of talc rock almost invariably includes the mining of asbestos as well, the asbestos contaminant is carried over into the consumer product and thus introduces the risk of asbestos disease (2).

Knowledge of diseases associeted with the use of asbestos apparently dates back 2000 years and detailed medical reports with the classification of asbestos as a harmful substance began about 1900 (3). It has been widely proven that the inhalation of asbestos is the direct cause of hemolysis (4,5,6) and diseases such as asbestosis, bronchial cancer, pleural mesothelioma and peritoneal mesothelioma (3,4,5,7,8,9,1

Asbestosis is a diffuse pulmonary fibrosis initiated by the inhalation of asbestos particles. The particles above 10 microns are filtered in the passage through the nose and trachea to the lungs, but the inhaled air reaching the respiratory bronchioles and alveoli contains thesmall-sized particles (1-5 microns) that would tend to

deposit (3). Timbrell found that the fibres of 3 microns diameter are the thickness that are likely to be deposited in the alveolar regions (11), and the fibres with a smaller diameter (less than 3 microns) -especially those below 1 micron- are carcinogenic if introduced into the pleural or peritoneal cavity (9). Neither the "cleanning" (mucociliatory escalator) nor the inmunological system (macrophages) are able to expell or destroy these particles (3,4,12). Then fibroblasts in an irreversible process produce the collagen, which forms the characteristic fibrosis of the asbestosis (5);these can lead torespiratory disability (5) and death may result from pulmonary hypertension and cardiac failure (3).

About 50% of the asbestosis patients may develop carcinoma, such as mesothelioma, a diffusive cancer that rapidly spreads over the surface of the lungs, abdominal organs and heart (3).

The exposure to talc dust has been shown to produce lung scarring, termed talcosis, and asbestos bodies are observed in lung tissues of individuals who die of talcosis (14). The "fibrous" talc appear to be more pathogenic than "platy" talc, so this disease is due to asbestos rather than talc (14,15). Timbrell found that due to their fibrous shape, asbestos particles remain airborne longer and show less tendency to sediment than granular microparticles of equivalent weight (16); this physical factor will increase the asbestos exposure of a person in an environment where talc has been recently used.

The asbestos diseases are due to occupational and non-occupational exposures (8,17); only 40.8% of the mesotheliomas found in patients of London Hospital from 1917 to 1964 were due to occupational exposures (8). Every body is affected by this air pollution, as has been demonstrated in lung studies done in France (18) and New York City (19 Permissible occupational exposure limits exist in several countries, in the USA, the Occupational Safety and Health Administration (OSHA) proposed in 1975 a non-occupational exposure limit of 5 fibers/ml for a period of 15 minutes (9).

Several mineralogical analyses have been made on commercial talc, and all the samples contained asbestosform mineral impurities (5,20). Snider et al in 1972 found that in eighteen commercial talcum powders, the asbestos impurities varied in amounts from 4 to 46% meanwile the labels listed no impurities (20). In 51 common talcs analysed at

Mount Sinai Hospital, the asbestos content ranged as high as 87% (5). The purity of any commercially available talc in the U.S. is related to both the nature of the original talc deposit and the extent to which the rock is upgraded to eliminate contaminant minerals. As the percentage of asbestos impurities is not related to price (20), this labeling will probably force the producers to control their talc composition to maintain their revenues.

There have been many lawsuits relating to the health aspects of asbestos, and the causes of action in product liability lawsuits generally involve the operative allegations:

-Failure to warn: thus the consumer was unaware of the danger.

-Failure to test: by the producers to test their products to properly ascertain its hazard, risk and dangers.

-Failure to remove: by the producers to stop selling, or remedy (make safe) the asbestos product (3). Warning of the health risks of exposure to asbestos has been recommended as a measure to be taken within the European Communities in 1977, and stated:

"Asbestos containing products should be clearly labelled" (9).

The Food, Drug and Cosmetic Act is clear about these facts:

> "If an article is alleged to be misbranded because the labeling is misleading, then in determining whether the labeling is misleading there shall be taken into account (among other things)...the extent to which the labeling fails to reveal facts material in light of such representations or material with respect to consequences which may result from the use prescribed in the labeling thereof or under the conditions of use as are customary or usual". (21 USCS § 321.n)
>
> "A cosmetic shall be deemed to be misbranded- (b)If in package form unless it bears a label containing (2) an accurate statement of the quantity of the contents in term of weight, measure, or numerical count." (21 USCS § 362)
>
> "A cosmetic shall be deemed to be adulterated- (a)If it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or under such conditions of use as are customary or usual." (21 USCS § 361)

Taking into account the widespread use of cosmetic talc, which starts at birth (mostly used in the first years of life) and continues in a great number of people as a periodic exposure throughout their lifespan, I address this petition to request the obligatory establishment of lables of quality (asbestos particle size) quantity (proportion of impurities) of components as well as a label of warning of the hazardous effects produced by asbestos with the continuous use of cosmetic talc.

Respectfully submitted,

Philippe Douillet
1 Holyoke Lane
Stony Brook, NY. 11790
(516) 751-5350

November 8,1983

References

1. Speil,S and J.P. Leineweber. 1969. Asbestos Minerals in Modern Technology. Environ. Res. 2:166-208.
2. Rohl,A.N. 1974. Asbestos in Talc. Environ. Hlth. Perspec.9:129-132.
3. Peters,G.A and B.J.Peters. 1980. Sourcebook on Asbestos Diseases: medical,legal and engineering aspects. Garland Press,NY.443p.
4. Harington,J.S.,A.C Allison and D.V. Badami. 1975. Mineral fibres: Chemical, Physicochemical and Biological Properties. Advan. Pharmacol. Chemother. 12:291-402.
5. Selikoff,I.J and D.H.K. Lee. 1978. Asbestos ans Disease. Academic Press, NY. 549p.
6. Light,W.G and E.T.Wei. 1977. Surface Charge and Hemolytic Activity of Asbestos. Environ. Res. 13:135-145.
7. Sawyer,R.N. 1977. Asbestos Exposure in a Yale Building. Environ. Res. 13:146-169.
8. Commitee on Biological Effects of Atmospheric Pollutants. 1971. Asbestos. The need for and feasibility of air pollution controls. National Academie of Sciences. 40p.
9. Report for the Commission of the European Communities. Public Health Risks of Exposure to Asbestos. 1977. Pergamon Press.149p.
10. Preger,L.,D.T. Arai.,P. Kotin.,H. Weill and J. Werchick. 1978. Asbestos-related Disease. Grune & Stratton Inc. 271p.
11. Timbrell,V. 1973. Physical factors as etiological mechanisms. In: Biological effects of Asbestos. Ed. P. Bogovski e.a. 295p.

12. Suzuki,Y. 1974. Interaction of Asbestos with Alveolar Cells. Environ. Hlth. Perspec. 9:241-252.
13. Langer, A.M. 1974. The subject of continuous vigilance. Environ. Hlth. Perspec. 9:53-56.
14. Rohl,A.N and A.M. Langer. 1974. Identification and quantification of Asbestos in Talc. Environ. Hlth. Perspec. 9:95-109.
15. Smither,W.J. 1974. Asbestos in the Work place and the Community. Environ. Hlth. Perspec. 9:327-329.
16. Timbrell,V. 1965. The inhalation of fibrous dusts. Ann. NY. Acad. Sci. 132,255.
17. Zolov,C.,T. Bourilkov and L. Badadjov. 1967. Pleural Asbestosis in Agricultural Workers. Environ. Res. 1:287-292.
18. Fondimare,A and J. Desbordes. Asbestos Bodies and Fibres in Lung Tissues. Environ. Hlth. Perspec. 9:147-148.
19. Langer,A.M.,Selikoff I.J and A. Sastre. 1971. Chrysolite asbestos in the lungs of persons in New York City. Arch. Environ. Health. 22:348.
20. Snider,D.W.,D. Epfeiffer and J.J. Mancuso. 1972. Asbestosform impurities in commercial talcum powders. Compass. 49,#2:65-67.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

C022.1a

Memorandum

Date May 21, 1985

From Robert Brown
BRAB, Division of Mathematics (HFF-118)

Subject Four methods of quantitating mesothelioma risk based on the Selikoff, et. al., insulation workers asbestos study. Technical support for QRAC's asbestos risk assessment.

To QRAC

In fig. 1 we have plotted on a log-log scale Selikoff's original mesothelioma incidence data vs. years since first exposure to asbestos. Incidence is defined as number of mesotheliomas/man-years exposure. The data do not seem to fit a single straight line. Uncertainties of exposure in the early part of the century and the general decline in intensity of asbestos exposure after World War II are possible sources of error. For these reasons, as well as general lack of fit of both recent data and distant past data, Peto recommended use of a more homogeneous subset of workers for quantitative purposes, namely those workers first exposed between 1922 and 1946 [8]. It can be inferred from Selikoff's report that this subset consists of about 4800 workers.

Peto reports 180 mesotheliomas (3.75%) among this subgroup out of a total of 236 mesotheliomas for all 17,800 workers followed from 1967 until about 1978 or 1979. Note that Selikoff only reported 175 mesotheliomas total; however, his reported follow-up period was also shorter (1967-1976).

Plotting Peto's homogeneous 1922-46 cohort subset, we see that $bt^{3.1}$ nicely fits the data (expressed as a straight line on log-log paper with a slope of 3.1). We also see that $b(t-10)^{2.1}$ nicely fits the data (with a different value for the constant b) and may be a reasonable

way of looking at mesotheliomas since the time lag from mesothelioma induction to death is not zero. The time of mesothelioma induction is not even a well defined concept and may be intimately entertwined with the concept of stage definition in, for example, a multistage cancer process. Nevertheless, both these model fits assume mesothelioma to be a nonincidental tumor (i.e., a life table where incidence is the ratio #tumor bearers/#survivors, re-expressed in man-years, per time interval). If we assume mesothelioma annual incidence to be better approximated by a prevalence or incidental definition, (#tumor bearers/#dead in interval), then $bt^{1.64}$ seems to be a rough though not very tight fit to the original Selikoff data. Peto's reported 1922-1946 data set does not easily allow determination of a prevalence fit. However, since the prevalence denominator is defined in terms of deaths per time interval rather than the much larger number of survivors to date, the first 2,271 deaths (12.7% of 17,800 workers) reported by Selikoff are very heavily weighted with the 1922-1946 cohort used exclusively in the two nonincidental curve fits above. Therefore comparisons of slightly different cohort subsets may still be useful. We estimate that the average time since first exposure for the Peto subset (1922-1946 first exposure) is about 37 years (Peto's 1978[+] follow-up) or 35 years (Selikoff's 1976 follow-up). This compares to 25 years average time since first exposure usually reported for all 17,800 workers. We also make the assumption that workers ceased exposure on average 3 years before death.