

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-587**

**PHARMACOLOGY REVIEW(S)**



**Previous Review(s), Date(s) and Reviewer(s):** none

**Studies Reviewed for this submission:**

**Pharmacology**

1. Bresticker, MA et al., Optimal pleurodesis: a comparison study. *Ann. Thor. Surg.* 1993; 55:364-367.
2. Mathlouti, A. et al., Etude anatopathologique experimentale du talcage pleurale. *Rev. Mal Resp.* 1992; 9:617-621.
3. Kennedy, L., et al., Talc slurry p[leurodesis: pleural fluid and histologic analysis. *Chest* 1995; 107:1707-1712.
4. Light, RW et al., Talc slurry is an effective pleural sclerosant in rabbits. *Chest* 1995; 107:1702-1706.
5. Henderson, W.J. et al., Ingestion of talc particles by cultured lung fibroblasts. *Environ. Res.* 1975, 9: 173-178.
6. Davies, R. et al., Cytotoxicity of talc for macrophages in vitro. *Fd. Chem. Toxic.* 1983, 21:201-207.
7. Ghio, A.J. et al., Role of surface complexed iron in oxidant generation and lung inflammation induced by silicates. *Am J. Physiol.* 1992, 263: :511-L518.

**Pharmacokinetics**

1. Phillips, J.C. et al., Studies on the absorption and disposition of 3H-labelled talc in the rat, mouse, guinea-pig and rabbit. *Food Cosmet. Toxicol.* 16:161-163, 1978.
2. Wehner, A.P. et al., Pulmonary deposition, translocation, and clearance of inhaled neutron-activated talc in hamsters. *Food Cosmet. Toxicol.* 15: 213-224., 1977.
3. Wehner, A.P. et al., Absorption of ingested talc by hamsters. *Food, Cosmet. Toxicol.* 15: 453-455, 1977.
4. Wehner et al., On talc translocation from the vagina to the oviducts and beyond. *Food Chem. Tox.* 24:329-338, 1986.
5. Hanson, RL et al., Method for determining the lung burden of talc in rats and mice after inhalation exposure to talc aerosols. *J. Appl. Toxicol.* 1985, 5: 283-287.

**Toxicology**

1. Davis, JMG, The fibrogenic effects of mineral dusts injected into the pleural cavity of mice. *Br. J. exp. Path.* 1972, 53: 190.
2. Wehner, A.P. et al., Inhalation of talc baby powder by hamsters. *Food Cosmet. Toxicol.* 15:121-129, 1977. USP monograph on Talc.
3. Pott, F et al., Tumorigenic effect of fibrous dusts in experimental animals. *Environ. Health Perspect.* 1974, 9:313-315.
4. Pelling D and KR Butterworth. Influence of the sterilization method and of magnesium oxide on the tissue responses in the rat to modified-starch glove powders. *J. Pharm. Pharmacol.* 1980, 32:757-760.
5. Sheikh, KM et al., An experimental histopathologic study of surgical glove powders. *Arch. Surg.* 1984, 119: 215-219.
6. Ozesmi, M. et al., Peritoneal mesothelioma and malignant lymphoma in mice caused by fibrous zeolite. *Br. J. Ind. Med.* 1985, 42:746-749.
7. Marusic, A et al., Talc granulomatosis in the rat: involvement in the acute-phase response. *Inflammation* 1990, 14:205.
8. IARC monograph: Talc. 1987.

**Reproductive Toxicology**

1. Food and Drug Research Laboratories. Teratologic evaluation of FDA 71-43 (TALC). National Technical Information Service. 1973.

## Genotoxicology

1. Endo-Capron, S. et al., In vitro response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair). Toxic. in vitro. 1993; 7:7-14.

**Studies Not Reviewed for this NDA:** none provided

**Studies Previously Reviewed for this NDA:** none

*Note: Portions of this review were excerpted directly from the sponsor's submission.*

## PHARMACOLOGY

1. Bresticker, MA et al., Optimal pleurodesis: a comparison study. Ann. Thor. Surg. 1993; 55:364-367.

Twenty five mongrel dogs were assigned to receive two of five methods of pleurodesis (one technique per side): 1) gauze abrasion, 2) 500 mg tetracycline, 3) 1 g talc poudrage, 4) Nd:YAG laser photocoagulation, or 5) argon beam electrocoagulation. After 30 days, the animals were observed for degree of adhesion on a 0 (no adhesion) to 4 (more than 1 lobe adheres to chest wall and mediastinum).

One dog receiving laser coagulation died on day 4 following operation with a massive hemothorax and a focal area of necrosis in the intercostal muscle overlying a neurovascular bundle. No other complications were noted. The grading for each technique is shown in the following table.

*Table 1. Results of Pleurodesis*

| Technique             | Grade <sup>a</sup>      |
|-----------------------|-------------------------|
| Mechanical abrasion   | 3.0 ± 0.82              |
| Talc poudrage         | 3.0 ± 0.67              |
| Tetracycline          | 2.3 ± 1.4               |
| Argon beam coagulator | 1.5 ± 0.97 <sup>b</sup> |
| Nd:YAG laser          | 0.7 ± 0.95 <sup>b</sup> |

<sup>a</sup> Values are shown as mean ± standard deviation. <sup>b</sup> p < 0.01 versus talc poudrage and mechanical abrasion.

Nd:YAG = neodymium:yttrium-aluminum garnet.

2. Mathlouti, A. et al., Etude anatopathologique experimentale du talcage pleurale. Rev. Mal Resp. 1992; 9:617-621.

Five mongrel dogs/group were administered intrapleural 1) saline, 2) 2 ml talc in saline or 4 ml talc granules. The talc was specified as sterilized Luzenac with low free silicates. Dogs were sacrificed on days 1, 3, 7, 15, or 30 and the pleural tissues examined microscopically.

There was no difference in extent or scope of damage with 2 vs. 4 ml talc. Three phases of damage were noted: days 1-3 was an exudative response, day 7 granulomatous reaction, and day 30 solid fibrous reaction. There was no penetration into the lung deeper than 3-4 mm. No damage to viscera outside the pleural cavity was noted.

3. Kennedy, L., et al., Talc slurry pleurodesis: pleural fluid and histologic analysis. Chest 1995; 107:1707-1712.

New Zealand white rabbits (28) were administered USP-asbestos-free talc at 70 mg/kg in 3 ml 0.9% saline. The dose was based on a 5 g dose in a 70 kg human. Rabbits were sacrificed on days 1, 2, 3, 7, 15, 30, 60, 90, or 120. The thorax was resected, the pleural fluid aspirated and cell counts made. Macro- and

microscopic examination was made of adhesions, lung, thoraces, liver, spleen, and kidneys.

At 24 and 48 hours post-dosing, 2.9 and 1.7 ml respectively of pleural fluid were observed. After 48 hours, 0.2 ml or less was found. Originally, neutrophils predominated in the pleural fluid, then monocytes and macrophages. Grossly, 0.5 to 10 mm grains of talc were noted in all rabbits. Fibrin strands were noted at all time points, sometimes associated with visible talc. Adhesions were thin and filmy prior to day 15. Complete pleural symphysis was not observed at any time point. On the microscopic level, at 24 hours, talc particles were associated with focal denudement of mesothelial cells with mononuclear cell infiltration. Patchy pleural thickening (peak day 3-7) was noted in all rabbits. Fibrin formed the core of the adhesions (positive staining for hyaluronic acid). Talc was also found microscopically in mediastinal lymph nodes (4/23), kidney (1/6), and spleen (4/10). No talc was found in the liver.

**4. Light, RW et al., Talc slurry is an effective pleural sclerosant in rabbits. Chest 1995; 107:1702-1706.**

The right lungs of male New Zealand white rabbits (10/dose) were collapsed surgically, then a slurry of 50, 100, 200 or 400 mg/kg talc (asbestos-free, Sigma) was instilled. Rabbits were necropsied on day 28 following instillation and the presence of hemothorax, the position of the mediastinum, the degree of pleurodesis (0=none, 4=complete obliteration of pleural space), and histopathology of the pleura and lung were examined. The controls were the left lungs of each rabbit. Note: the observers were blinded as to the dose of talc of each rabbit.

No rabbits died prior to scheduled sacrifice. No hemothorax, mediastinal shift, or atelectasis of the lungs were observed. Pleurodesis was more complete in spaces where talc had collected. Additionally, the degree of pleurodesis increased in a dose dependent manner to a maximum mean score of  $3.36 \pm 0.48$ . Similar dose dependent increases in microscopic fibrosis and inflammation were noted. Fibrosis and inflammation of the lung itself did not increase to a significant extent above controls at any dose.

**Table 1—Mean Values for Gross Pleurodesis Score and Microscopic Pleural Fibrosis and Inflammation With the Four Different Doses of Talc and on the Control Side**

| Dose of Talc,<br>mg/kg | n  | Gross Pleurodesis       | Microscopic Fibrosis | Microscopic Inflammation |
|------------------------|----|-------------------------|----------------------|--------------------------|
| Control (left)         | 44 | $0.0 \pm 0.0^*$         | $0.39 \pm 0.61^*$    | $0.75 \pm 0.68^*$        |
| 50                     | 11 | $1.09 \pm 0.90^\dagger$ | $1.82 \pm 0.57^*$    | $1.64 \pm 0.77^\dagger$  |
| 100                    | 11 | $1.55 \pm 1.08^\dagger$ | $2.09 \pm 0.67^*$    | $1.82 \pm 0.39$          |
| 200                    | 11 | $2.73 \pm 0.62$         | $2.55 \pm 0.78$      | $1.64 \pm 0.48^\dagger$  |
| 400                    | 11 | $3.36 \pm 0.48$         | $3.27 \pm 0.86$      | $2.36 \pm 0.64$          |

\* $p < 0.01$  when compared with 400 mg/kg.

† $p < 0.05$  when compared with 400 mg/kg.

**5. Henderson, W.J. et al., Ingestion of talc particles by cultured lung fibroblasts. Environ. Res. 1975, 9: 173-178.**

Rabbit lung fibroblasts in culture were exposed to talc (Italian, 00000) for 4-5, 26 hours, and 8 days. Cells were examined by electron microscope. Talc penetrated the cell membrane, but not the nuclear membrane. The cell membrane had a "fuzzy" appearance when in contact with the talc particle similar to that observed with pinocytosis.

**6. Davies, R. et al., Cytotoxicity of talc for macrophages in vitro. Fd. Chem. Toxic. 1983, 21:201-207.**

Mouse peritoneal macrophages were exposed to up to 150 ug/ml talc for 2-3 hours in quadruplicate. The talc was either from Spain, Italy, China, France or Australia. Cytotoxicity was assessed by measuring LDH and BGLU (lysosomal  $\beta$ -glucuronidase) release into the medium and comparing that to the release with DQ12 quartz, magnetite as negative control.

All of the samples of talc analyzed were 1/10th to 1/5th as toxic to macrophages as quartz.

Table 3. Toxicity of various talcs relative to that of DQ12 using log (M/C) transformation\*

| Dust                     | Estimated relative toxicity<br>(with 95% confidence limits) |
|--------------------------|---|
| Magnetite                | -0.001 (-0.030 0.026)                                       |
| Talcs                    |   |
| Indian Finex             | 0.090 (0.064 0.116)   |
| Italian 00000 micronised | 0.160 (0.134 0.187)   |
| Chinese (Haichen) No. 1  | 0.102 (0.076 0.128)   |
| Spanish SS               | 0.110 (0.084 0.136)   |
| French OXO               | 0.117 (0.088 0.146)   |
| Italian 00000            | 0.132 (0.106 0.158)   |
| Australian West Side     | 0.135 (0.109 0.161)   |

\*Experimental section.

7. Ghio, A.J. et al., Role of surface complexed iron in oxidant generation and lung inflammation induced by silicates. *Am J. Physiol.* 1992, 263: :511-L518.

Talc (and other silicates) complex iron on their surface. The amount of complexed iron is proportionally associated with oxidant generation, the inflammation process, macrophage respiratory burst, and leukotriene release by macrophages.

#### Summary of Pharmacology

Several experiments were performed in rabbits and dogs to compare the degree of pleurodesis with talc and other minerals. At least one experiment used talc mined from the Luzenac facility. In the dog, no difference in degree of adhesion was noted with 2 versus 4 ml talc; however, the rabbit did show a dose dependent increase in adhesion with increasing talc concentration. The process observed was macrophage/monocyte infiltration, followed by a collagenous fibrotic response over the next two weeks. Granules of talc were detectable during all observation times up to 120 days. Only one experiment showed any microscopic talc outside the pleural cavity (mediastinal lymph nodes and kidney).

At the cellular level, talc had minimal cytotoxicity against macrophages. Granules appeared to enter the cells through a pinocytotic-like process. The actual inflammation process may be associated with the iron complexed to the mineral its effects on free radical generation.

**SAFETY PHARMACOLOGY** none submitted

#### PHARMACOKINETICS AND TOXICOKINETICS:

1. Phillips, J.C. et al., Studies on the absorption and disposition of 3H-labelled talc in the rat, mouse, guinea-pig and rabbit. *Food Cosmet. Toxicol.* 16:161-163, 1978.

Tritium labelled talc was administered by oral gavage to either rats (50 mg/kg as a single dose or daily X 6), guinea pigs (25 mg/kg single dose), or mice (40 mg/kg); rabbits were administered 0.5 ml of talc solution intravaginally. In the rat and guinea pig, urine and feces were sampled up through day 10, liver, kidneys, gi tract were also examined at termination (day 10). The mice were sacrificed at 6 and 24 hours and the gi tract (and contents) examined. Finally, rabbits treated intravaginally had urine collected over 24 hour intervals for 3 days, then were killed and the urogenital tract radioactivity determined. LSC was used to measure radioactivity.

With sc. injection of talc into rats, 97.3 to 99.4% of the radioactivity was recovered from the resulting granuloma at day 5. With single or daily X 6 oral administration to the rat, approximately 75% of the radioactivity talc was recovered in the feces, and an additional 1% in the urine within the first 24 hours. By

96 hours,  $97.5\% \pm 10.3\%$  was recovered from the urine and feces (less than 2% in urine). No radioactivity was found in the liver or kidneys at day 10. Similar results were obtained in the guinea pig and mouse. With intravaginal administration in the rabbit for up to 6 days, less than 0.04% of the radioactivity was found at the site of injection and less than 1/5th was found at the fallopian tubes.

**2. Wehner, A.P. et al., Pulmonary deposition, translocation, and clearance of inhaled neutron-activated talc in hamsters. Food Cosmet. Toxicol. 15: 213-224., 1977.**

Johnson's baby powder (Vermont talc, lot # 228p) was exposed to an integrated neutron flux to produce radionuclides for tracking. Female Syrian golden hamsters (44 10 week old animals) were exposed to talc (nose only) for 2 hours. The estimated dose was 360 ug talc. Hamsters were sacrificed at 15, and 100 minutes, 4, 21 hours, 2, 4, 8, 19, 36, 68 and 132 days later. Lungs, liver, kidneys, carcass, ovaries, urine and feces were analyzed for isotopes.

In the lungs, the measurements of talc by the  $^{60}\text{Co}$  were variable depending on the position in the exposure chamber. However, the authors estimated the half-life of talc in the lung to be between 7 and 10 days, with complete clearance within 4 months. There were no significant differences in liver, ovarian or kidney talc content between treated and controls. Carcasses had an elevated radioactivity level with declined by 20 fold over 4 days following exposure. This may be associated with the fecal excretion of ingested talc., as at 4 days 4% of the total radioactivity was in the lung, 4% in the carcass, 91% in the feces, and 1% in the urine (which may be due to contamination by feces).

**3. Wehner, A.P. et al., Absorption of ingested talc by hamsters. Food, Cosmet. Toxicol. 15: 453-455, 1977.**

Johnson's baby powder (Vermont talc, lot # 228p) was exposed to an integrated neutron flux to produce radionuclides for tracking. Female Syrian golden hamsters (44 10 week old animals) were administered oral gavage talc in 1% methyl cellulose/physiologic saline at 2.94 mg /hamster. Hamsters were sacrificed at 24 hours post-dose and the lungs, liver, kidneys, carcass, ovaries, urine and feces were analyzed for isotopes by counting  $^{60}\text{Co}$   $\gamma$  radiation.

Approximately 98% of the administered radioactivity was found in the feces and gastrointestinal tract (74 and 24% respectively). No significant difference in radioactivity between control and talc treated radioactivity levels were found in the urine, liver, lungs or kidneys.

**4. Wehner et al., On talc translocation from the vagina to the oviducts and beyond. Food Chem. Tox. 24:329-338, 1986.**

Johnson's baby powder (Vermont talc, lot # 228p) was exposed to an integrated neutron flux to produce radionuclides for tracking. Female cynomolgus monkeys (4-12 years old, multiparous) were administered 125 mg talc in physiologic saline/1% methylcellulose to the posterior fornix of the vagina for 30 consecutive workdays. Two days after the 30th dose, peritoneal lavage fluid, ovaries, oviducts, uterus, cervix, vagina were collected and analyzed for the presence of  $^{60}\text{Co}$   $\gamma$  radiation.

Essentially no talc was found anywhere other than in the vagina/cervix.

**5. Hanson, RL et al., Method for determining the lung burden of talc in rats and mice after inhalation exposure to talc aerosols. J. Appl. Toxicol. 1985, 5: 283-287.**

The burden of inhaled talc was determined by measuring the acid-insoluble fraction of magnesium (natural component of talc). Mice or rats were exposed to aerosolized talc for 6 hrs/day, 5 days/week for 4 weeks at 0, 2, 6, or 18 mg/m<sup>3</sup>.

The lower limit of detection was 0.1 ppm; magnesium recovery was > 89%. The background level of Mg was 0.5 ug/g lung in young animals and 3-6 ug/g lung in 12-18 month old animals. Lung talc concentration was relatively linear with dose, with maximum levels of  $806 \pm 135$  and  $1150 \pm 101$  ug/g lung in rat and mouse respectively 17-20 mg/m<sup>3</sup> talc.

### Summary and Evaluation of Preclinical Pharmacokinetics

Essentially, talc is not bioavailable. When administered orally, it is excreted in the feces. When inhaled, it is pushed out by the ciliary action of the airways. And, when administered by the sc route, which most resembles the intrapleural route, >98% can be recovered from the injection site. The results were reproducible in mouse, rat, hamster and guinea pig. The IARC monograph on talc pointed out the relative insensitivity of the detection methods; however, the findings still suggest that only extremely minimal amounts of talc are systemically available.

### **TOXICOLOGY**

#### **1. Davis, JMG, The fibrogenic effects of mineral dusts injected into the pleural cavity of mice. Br. J. exp. Path. 1972, 53: 190.**

Balb/c mice (25/sample) were administered 10 mg talc in 0.5 ml distilled water into the upper right pleural cavity. Other minerals tested included asbestos (chrysotile, brucite, chlorite, chromite, forsterite, magnetite, olivine, pyroxene, and serpentine. Effects of size were also investigated by grinding the minerals and sieving through various meshes. Mice were observed from 2 weeks to 18 months for pleural lesions (gross and microscopic observation). The description stated that the talc was mixed with small quantities of asbestos fibers 0.05-0.5 um in diameter X 2 um in length.

No data on changes in clinical observations, hematology or serum chemistry, or a description of the fate, histopathology or gross changes in individuals or groups were included. Although the time frame was not specified, granulomas attached to lung and pleura were quickly and extensively formed with talc. Collagen was produced in all surface layers and, over the course of 6-8 months, infiltrating cells were replaced by collagen. The authors noted that talc was the only non-fibrous dust to produce adhesions.

#### **2. Wehner, A.P. et al., Inhalation of talc baby powder by hamsters. Food Cosmet. Toxicol. 15:121-129, 1977.**

Fifty 4-week old Syrian golden hamsters/sex/group were exposed to aerosol talc for 3, 30, or 150 min/day with a mean total aerosol concentration of 37.1 ug/L, respirable fraction 9.8 ug/L for 30 days. A second set of 25 7-week old hamsters/sex/dose were exposed to 30 or 150 min/day of talc at 27.4 ug/L, respirable fraction 8.1 ug/L for 300 days. Johnson's baby powder (Vermont talc, 95% platy talc, trace magnesite, dolomite, chlorite and rutile) lot 228p was used for the aerosol; controls were room air. The cumulative exposures were 12, 120, and 600 mg hr/m<sup>3</sup> for the 30 day groups, and 1200, 6000 mg hr/m<sup>3</sup> for the 300 day groups. At the end of their lifespan, or when mortality in any group reached 90%, a necropsy was performed and the lungs, trachea, larynx, heart, liver kidney, stomach, ovary, uterus, and testes were examined microscopically. Lung tissue was also examined by scanning EM and X-ray to determine the talc load.

No significant differences in behavior was noted between treated and controls. Lifespan and body weight did not differ significantly between controls and talc-treated hamsters. However, most of the hamsters were dead by 20 months. No dose dependent changes in probit curves were noted with treatment. While there were no significant dose or time dependent increase in the incidence of lung histologic damage (alveolar emphysema, interstitial pneumonia, calcification, and alveolar hyperplasia/histiocytosis); all doses increased the incidence of these findings 2-5 fold above controls. Focal calcification of the trachea, stomach mucosa was noted in both treated and control hamsters. No significant incidence of neoplasms at any site was noted.

#### **3. Pott, F et al., Tumorigenic effect of fibrous dusts in experimental animals. Environ. Health Perspect. 1974, 9:313-315.**

Four weekly i.p. injections of 25 mg talc were made to 40 rats. Only time to tumor, tumor type and tumor rate were reported. The first tumors with talc were noted on day 587 and the rate was 2.5%. The authors stated that nearly all the tumors were sarcomatous mesotheliomata. Chrysotile A at the same dose led to first tumors at day 270 and a 37.5% incidence.

4. Pelling, D and KR Butterworth. Influence of the sterilization method and of magnesium oxide on the tissue responses in the rat to modified starch glove powders. *J. Pharm. Pharmacol.* 1980, 32:757-760.

In female Wistar rats (16/group), 17.4 mg talc, approximately 50 mg starch powder, or 7.7 mg magnesium oxide were sprinkled over the abdominal viscera. Rats were sacrificed on either day 7 or 14 and the viscera examined for granulomas. The talc was provided by Luzenac (stearic 'O' talc).

The incidence of adhesions with talc at day 7 and 14 was approximately 6- fold higher than that in the sham operated controls. The incidence of granulomas was maximal, in that the authors stopped counting granulomas at 30/animal, and the incidence was 30 at both day 7 and 14.

5. Sheikh, KM et al., An experimental histopathologic study of surgical glove powders. *Arch. Surg.* 1984, 119: 215-219.

In male Sprague Dawley rats, incisions were made in the abdominal muscle and either 3 X 2 mm pellets of Biosorb (cornstarch with magnesium oxide) or talc were implanted or suture material dusted with biosorb or talc were implanted (6 implant sites/rat). Rats were sacrificed on days 1, 2, 3, 4 or 5 and on weeks 1, 2, 4, 6, 8, or 12. The implant sites were examined microscopically.

Suture dusted with a talc showed a white fibrous area around the implant in 2/5 rats at 4 and 8 weeks. Talc pellets were visible at all time points. Granulomas had formed by day 3. The histopathology is summarized in the following table.

| Summary of Histologic Examination Results |   |   |
|---|---|---|
|   | Keeffe  | Talc  |
|   |   | Pellets   |
| Day 1                                     | Severe acute inflammation with edema; polymorphonuclear leukocytes predominate; uniform dispersion of starch granules within exudate  | Acute inflammatory response, mild to moderate; reaction confined mainly at periphery of talc pellet; mild edema   |
| Day 3                                     | Decreased acute inflammatory reaction; condensation of fibrin around starch particles; minimal edema; beginning of nuclear fragmentation and early granulation tissue formation | Early giant-cell reaction immediately surrounding talc pellet; occasional eosinophil noted; polymorphonuclear leukocytes markedly decreased                                     |
| Day 5                                     | Chronic inflammation with maturing granulation tissue, mostly histiocytes and few lymphocytes; starch material not visible  | Pellet still present; well-defined granuloma now visible; some giant cells show inclusion of talc particles; increased number of eosinophils and plasma cells noted             |
| 8 Weeks                                   | Mild chronic inflammation with minimal fibrosis   | Moderate amount of talc material, increased fibrous tissue formation surrounding pellet; few well-formed granulomas still seen  |
| 12 Weeks                                  | Occasional atrophic muscle fibers surrounded by minimal fibrous tissue; complete restitution of original tissue   | Well-defined fibrous capsule around talc tablet; occasional giant cell containing talc particle visible in wall   |
|   |   | Sutures   |
| Week 1                                    | Chronic histiocytic response around suture material, with plump-looking histiocytes and fibroblasts; lymphocytes and few plasma cells noted                                     | Chronic histiocytic response around suture material; in close proximity to sutures scattered birefringent talc granules of various sizes are present; giant-cell formation seen |
| Week 4                                    | Minimal inflammation, mostly lymphocytes and relatively few histiocytes   | Prominent giant-cell formation around suture material; histiocytes, fibroblasts, and lymphocytes present with presence of talc crystals   |
| Week 12                                   | Fibrous capsule around suture; very minimal response, with few eosinophils  | Histiocytic response, with persistent giant cells surrounding birefringent crystals, occasional eosinophils   |

6. Ozesmi, M. et al., Peritoneal mesothelioma and malignant lymphoma in mice caused by fibrous zeolite. *Br. J. Ind. Med.* 1985, 42:746-749.

Six week old albino Swiss mice were administered 20 mg talc (commercial) intraperitoneally; zeolite at 5, 10, 20, 30 or 40 g and physiologic saline were also investigated. Animals were observed daily until death or obvious tumor burden. Animals were necropsied and the injection site, parietal and visceral peritoneal mesothelium, peritoneal lymph nodes, spleen, liver, kidneys, adrenals mediastinal lymph nodes and all tumors

were observed microscopically.

In the mice treated with zeolite, there was no correspondence between dose and tumor incidence. Overall incidence for tumors in those mice which survived past 6 months, was 26.1% in the zeolite group (84/321, primarily mesothelioma and lymphoma), 8.7% in the saline group (4/46, mesothelioma and lymphoma) and 12.5% in the talc group (3/24, mesothelioma only. The percentage mortality prior to 6 months was 70/391 in the zeolite groups (18%), 16/40 in the talc group (40%) and 16% in the saline controls. No explanation for deaths was given.

**7. Marusic, A et al., Talc granulomatosis in the rat: involvement in the acute-phase response. Inflammation 1990, 14:205.**

To investigate the acute phase response to talc granulomatosis, female Fischer rats, 8-10 weeks old, were injected s.c. with sterile talc (Merck, Darmstadt, F.R.G) at 800 mg/ml (1 ml) at 2-4 locations on the back. Body weight and clinical signs were monitored daily while hematology and serum chemistry were performed at 5 and 15 hours post dose, and on days 3, 7, 14, and 21. At sacrifice, the injection site and the proximal ends of the right tibia were also examined.

At the site of injection, monocyte and polymorphonuclear leukocyte infiltration was observed by day 3. By day 7, macrophages, neovascularization and fibrosis was noted with decreasing monocyte/polymorphonuclear cells. At 2 and 3 weeks, fibrosis increased and crystals were either encased in a fibrous envelope or in irregular giant multinuclear cells.

The following table summarizes the changes in parameters in serum and in the granuloma itself. In the liver, the zinc concentration increase by 30% from 15 hours through day 7; no changes in zinc levels were noted in the spleen. No significant changes in calcium or copper were noted in the liver or spleen. The percentage of osteoblasts on the trabecular surface of the tibia decreased time dependently with a nadir at day 14 (>98% decrease from controls), but levels of osteoblasts had rebounded to a 50% reduction vs. controls by day 21.

| Parameter | Serum    |                     | Granuloma |                     |
|-----------|----------|---------------------|-----------|---------------------|
|           | % change | day of nadir/zenith | % change  | day of nadir/zenith |
| Zinc      | 50%↓     | 15 hrs.             | ----      | ---                 |
| Copper    | 2-3X*    | days 3-21           | 5X†       | day 14              |
| Calcium   | nd       |                     | 5-6X†     | days 7, 14          |
| Iron      | 50%↓     | day 7               | nd        |                     |
| ACTH      | 4X*      | day 3, 7            | nd        |                     |
| ALP       | 3-5X*    | day 7, 14           | nd        |                     |

--- no significant difference, nd not measured

**8. IARC monograph: Talc. 1987. (International Agency for Research on Cancer)**

The monograph, written by committee, is a discussion of the papers published on talc up through 1987. Included are mining data, acute and chronic animal exposure by several routes including inhalation, oral and intrapleural, carcinogenicity results, and reproductive toxicity studies, as well as human epidemiology and clinical studies. The committee's conclusions on the carcinogenicity studies were that they were too short in duration, and that it was not clear that the form of talc used were free of asbestos contamination.

**Summary and Evaluation of Preclinical Toxicology:**

The major difficulty with talc for pleurodesis lies in finding studies with a relevant route of administration. Due to the low bioavailability, either i.p. or implantation (including sprinkling over viscera) are the most relevant routes. Again, the source of the talc and degree of contamination with asbestos are problematic, particularly for articles prior to the mid 1970's.

The process of granuloma formation following talc administration by sprinkling, muscle implantation or sc injection was similar, as was the response in rats and mice. During the initial day or two, monocytes and polymorphonuclear cells infiltrated the area near the talc. By day 3, macrophages were present and granuloma formation had begun. By two weeks through 12 weeks, a progressively fibrotic capsule/adhesion formed around the talc with increasing collagen content. Only one experiment addressed changes in clinical chemistry in the serum and granuloma: copper levels increased in both the serum and granuloma, calcium levels increased in the granuloma only (and were associated with decreased osteoblast number), while ALP levels increased in serum (probably associated with the muscle trauma from the injection). Over the observation periods of up to 12 weeks, talc was always visibly present.

Chronic studies or at least studies with long observation periods after talc administration by either sc, ip or implantation were performed. A single dose ip study with observations through death in the mouse at approximately 1.7 g/m<sup>2</sup> gave a mesothelioma incidence of 3/24 (controls, 4/46); however, the mortality was unacceptably high. In the rat, ip administration of a single dose level (333 mg/m<sup>2</sup>) for 4 weekly doses resulted in a tumor incidence of 2.5%; significantly lower than with asbestos, but relationship to controls unknown. Aerosolized talc for up to 300 days did not alter body weight or tumor incidence, although other lung pathology was increased. This particular experiment was not relevant to the indication at hand.

**Reproductive Toxicity:****1. Food and Drug Research Laboratories. Teratologic evaluation of FDA 71-43 (TALC). National Technical Information Service. 1973.**

The study was performed prior to GLP regulations. Presumed pregnant Dutch-belted female rabbits (14-29 does/group) were administered talc by oral gavage in a corn oil suspension on days 6-18 of pregnancy. Doses of talc were 9, 42, 195 and 900 mg/kg/day; controls were corn oil, positive controls were 2.5 mg/kg of 6-aminonicotinamide on day 9. Does were sacrificed on day 29 of pregnancy.

**Measurements and Observations:**

Days 0, 6, 12, 18, 29: maternal weight

Daily: clinical signs and food consumption

Termination: corpora lutea, implantation sites, resorption sites, live and dead fetuses, fetal body weight, gross anomalies, 24 hour survival, visceral and skeletal anomalies.

**Maternal observations:**

The maternal mortality and pregnancy data is summarized in the following table. Death and pregnancy at term did not correlate completely with increasing dose. Death also did not correlate with pregnancy status (pregnant vs. non-pregnant). Maternal body weight was decreased at 42 and 900 mg/kg, but not at 195 mg/kg. No description of clinical signs or necropsy data were included in the report.

| Treatment | # mated | #surviving @ term | day of death (P/NP) <sup>&amp;</sup> | #pregnant @term | Change in body weight kg (% vs. C) * |
|-----------|---------|-------------------|--------------------------------------|-----------------|--------------------------------------|
| Control   | 14      | 12 (86%)          | 21,26 (1/1)                          | 7 (58%)         | +0.24                                |
| 6-AN      | 14      | 12 (86%)          | 16,22 (1/1)                          | 8 (67%)         | +0.30 (+25%)                         |
| 9 mg/kg   | 25      | 20 (80%)          | 10, 12, 16, 18 (4/1)                 | 11 (55%)        | +0.35 (+46%)                         |
| 42 mg/kg  | 23      | 19 (83%)          | 10,11,12,21(2/2)                     | 10 (53%)        | +0.18 (-25%)                         |
| 195 mg/kg | 29      | 22 (76%)          | 15,16, 18,24,26,27(4/2)              | 10 (45%)        | +0.24 ---                            |
| 900 mg/kg | 15      | 13 (87%)          | 13,18 (2/0)                          | 11 (85%)        | +0.17 (-29%)                         |

& P/NP = # pregnant that died prior to term /# non-pregnant dying prior to term

\* body weight changes computed only on pregnant dams

Fetal observations:

The litter data (including corpora lutea #, implantations, and live/dead fetuses) are shown in the following table. There were distinct increases in the # of litters completely resorbed in the positive control and 900 mg/kg groups. Only the 900 mg/kg group had dead fetuses. One controls fetus had encephalocele, 9 6-AN (positive control) fetuses had malformations including anophthalmia, cleft palate, short tail, and club foot, while 2 900 mg/kg fetuses had short tails. Skeletal defects noted at increased frequency above control in the talc treated rats were extra sternebrae noted at control, 9, 42, and 195 mg/kg at 1/1, 2/2, 5/4 and 4/3 fetuses/# litters respectively. Positive controls showed a number of changes in the sternebrae, ribs, skull, and vertebrae.

| Group:                             | 171  | 172    | 173  | 174  | 175   | 176   |
|------------------------------------|------|--------|------|------|-------|-------|
| Dose (mg/kg):                      | Sham | 6-AN** | 9.0  | 42.0 | 195.0 | 900.0 |
| <b>Pregnancies</b>                 |      |        |      |      |       |       |
| Total No.                          | 8    | 9      | 15   | 12   | 15    | 13    |
| Med or Aborted (before Day 29)     | 1    | 1      | 4    | 2    | 5     | 2     |
| To term (on Day 29)                | 7    | 8      | 11   | 10   | 10    | 11    |
| <b>Corpora Lutea</b>               |      |        |      |      |       |       |
| Total No.                          | 221  | 193    | 242  | 279  | 276   | 195   |
| Average/dam mated                  | 15.8 | 14.2   | 10.5 | 12.1 | 9.52  | 13.0  |
| <b>Live Litters</b>                |      |        |      |      |       |       |
| Total No.*                         | 6    | 6      | 10   | 8    | 10    | 7     |
| <b>Implant Sites</b>               |      |        |      |      |       |       |
| Total No.                          | 47   | 36     | 51   | 42   | 51    | 41    |
| Average/litter*                    | 8.72 | 6.00   | 5.10 | 4.20 | 5.10  | 4.00  |
| <b>Resorptions</b>                 |      |        |      |      |       |       |
| Total No.*                         | 19   | 7      | 16   | 15   | 5     | 16    |
| Dams with 1 or more sites resorbed | 4    | 4      | 6    | 6    | 1     | 7     |
| Dams with all sites resorbed       | 1    | 2      | 1    | 2    | --    | 4     |
| Per cent partial resorptions       | 57.1 | 50.0   | 56.5 | 60.0 | 10.0  | 57.5  |
| Per cent complete resorptions      | 14.3 | 25.0   | 12.0 | 20.0 | --    | 15.4  |
| <b>Live Fetuses</b>                |      |        |      |      |       |       |
| Total No.                          | 29   | 40     | 37   | 27   | 46    | 23    |
| Average/dam*                       | 4.60 | 6.67   | 4.27 | 3.70 | 4.60  | 2.00  |
| Sex ratio (M/F)                    | 0.87 | 0.23   | 0.30 | 1.25 | 1.00  | 1.11  |
| <b>Dead Fetuses</b>                |      |        |      |      |       |       |
| Total No.*                         | --   | --     | --   | --   | --    | 5     |
| Dams with 1 or more dead           | --   | --     | --   | --   | --    | 2     |
| Dams with all dead                 | --   | --     | --   | --   | --    | 1     |
| Per cent partial dead              | --   | --     | --   | --   | --    | 13.2  |
| Per cent all dead                  | --   | --     | --   | --   | --    | 2.2   |
| <b>Average Fetus Weight, g</b>     | 15.6 | 24.9   | 13.3 | 41.1 | 17.5  | 17.5  |

**Summary and Evaluation of Reproductive toxicology:**

Basically, the study is of poor quality (incomplete data, large numbers of maternal deaths even in controls) with a irrelevant (oral, non-bioavailable) route. The proposed human route, intrapleural infusion, did not result in systemic exposure in animal experiments. In view of this data, it is not clear if any route of administration would be relevant to reproductive toxicity. Maternal death did not correlate with increasing talc dose. Body weight gain was significantly decreased in the 900 mg/kg (highest dose) dams only. In the dams with significant body weight gain decrement, a significant increase in fetal mortality was noted. Skeletal anomalies were noted at all talc doses. Malformation (short tail) was noted only in the 900 mg/kg talc fetuses. Thus, as malformations were only noted at maternally toxic doses, and the drug is not absorbed, talc should not be considered a teratogen.

**Genetic Toxicity:**

1. Endo-Capron, S. et al., In vitro response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair). *Toxic. in vitro.* 1993; 7:7-14.

The test cell system was rat pleural mesothelial cells (RPMC) between passages 5 and 15. Talc was obtained from Eurotalc (French #7841, Italian #5726 and Spanish # 5725 sources); agnathous and attapulgitte were used as negative references while Rhodesian chrysotile and crocidolite were used as positive controls. The structure of the RPMC's was examined by electron microscopy 24 hours following exposure to 10 ug/cm<sup>2</sup> or 50 ug/ml talc. UDS was investigated in sixuplicate after 24 hours with 0, 10, 20, or 50 ug/cm<sup>2</sup> (50, 100, or 250 ug/ml) talc. SCE's were measured after 48 hours of incubation with 2, 5, 10 or 15 ug/cm<sup>2</sup> (15, 37.5, 75, or 112.5 ug/ml) talc, with positive and negative controls.

Approximately 95% of the talc particles from Eurotalc were less than 6 um. No asbestos was found in these samples by microscope. No morphologic changes or cytolysis was noted. There were no statistically significant increases in the thymidine incorporation (UDS) while crocidolite and chrysotile asbestos increased UDS by 10-60% at up to 10 ug/cm<sup>2</sup>. The number of sister chromatid exchanges did not increase to a statistically significant extent with up to 15 ug/cm<sup>2</sup>, while with mitomycin C or chromate SCE's increased by 2-4 fold above control. Asbestos increased the SCE's by 13-25%.

**Summary and Evaluation of Genetic toxicology:**

No changes in chromosomes or repair was noted in a rat pleural epithelium model with up to 250 ug/ml talc. In the IARC committee review of the talc data it was state that the Ames test in the TA1530 strain, *Saccharomyces cerevisiae* D3, and host-mediated assays in mice were negative for mutagenesis. In vitro chromosomal aberration experiments using human cells were also negative and up to 500 mg/kg talc in the rat by the oral route did not result in changes in the dominant lethal assay. Details of these experiments are unavailable. From the limited data, talc does not appear to be mutagenic.

**OVERALL-SUMMARY AND EVALUATION**

From the published experiments designed to evaluate the pleurodesis effect in rabbits and dogs, as well as experiments on the effects of talc glove powders in rats, it is clear that talc causes a localized fibrotic reaction. Within 3 days, granulomas form, with fibrotic activity observed by 2 weeks following talc. Additionally, from measurements of radiolabeled talc as well as observations of white powder in the lungs after pleurodesis with talc, the compound is inert; it is not absorbed from the gi tract, lungs, or vagina. In one rabbit experiment, small quantities of talc were found in the kidneys, mediastinal lymph nodes, and spleen; however, this might be due to lymphatic clearance. Talc can be macroscopically observed for at least 120 days (longest timepoint) following administration.

A large number of talc carcinogenicity studies were performed prior to the 1980's by routes including oral, i.p., inhalation, and intrapleural administration. Most of these studies do not specify the actual type of talc used, or the degree of asbestos contamination. Interpretation is also difficult due to the limited

frequency/time frame of administration, usually less than 1 year. However, asbestos causes mesotheliomas in the animal models within 1 year of administration. No significant increase of tumor incidence above controls was noted in any study. Additionally, all in vitro studies reported were negative, although most of the data was not available for assessment. No impairment of fertility data was available. Although the sponsor stated that reproductive toxicity studies had been performed in several species, only the rabbit data could be audited. The oral-delivery rabbit study showed malformations only at maternally toxic doses. Maternal deaths were noted at all talc doses as well as in controls, suggesting a poorly conducted experiment. However, talc was not expected to be bioavailable by the oral route.

**RECOMMENDATION**

The NDA is approvable for Pharmacology/Toxicology

**NDA issues:****Labelling Review:**

With the currently available information, the changes in labelling are detailed below.

**Information for Investigator's Brochure/Informed Consent:**

To be marketed product issues (NDA only): Impurities, Extractables, and Excipients.

**Draft Letter to the Sponsor:**

File Name: Q N/I/PL/PM # /\_\_./

\_\_\_\_\_  
Wendelyn J. Schmidt, Ph.D.  
Pharmacologist/Toxicologist

**ISI**

- Original IND/NDA/DMF
- c.c. /Division File
- /JDeGeorge, Pharmacology Team Leader
- /Medical Officer
- /C.S.O.
- /WSchmidt, Reviewer
- /Pharmacology-Toxicology Assistant Director (NDA only)

*WJ Schmidt* 12/18/05