Summary of Health Data for
DOW CORNING™ C6-235 Elastomer

SUMMARY

The cured material was tested to determine potential to cause dermal sensitization, and cytotoxicity, as well as local and systemic effects in a USP Class V test and a short-term implant test. When tested directly or by extract exposure, the material was not a skin sensitizer. The material passed the systemic and intracutaneous reactivity tests that compose the USP Class V test and also met the requirements of 30-day implant study (with interim sacrifice period) in rabbits.

Note: The toxicology information in this data sheet is limited to that which is specified to meet C6 standards. Additional toxicology information, if available, may be provided to you upon request for an additional charge.

TOXICOLOGY DATA

Acute Toxicity

Skin Sensitization. The cured test article was tested for skin sensitization potential in guinea pigs in a modified Buehler test. Guinea pigs were exposed to the test article (solid), or extracts of the test article prepared in 0.9% Sodium Chloride for Injection (SCI), or acetone. The extracts were prepared at a ratio of 3-cm^2 of test article per ml of extractant. The SCI extracts were prepared by heating at 121±2 °C for 60 minutes in an autoclave, and the acetone extracts were prepared by heating at 70±2 °C for 24 hours in an incubator. An irritation screen in 2 guinea pigs was conducted to determine the irritation potential of the solid test article, the SCI and acetone extracts (100%) of the test article, and the extraction medium (acetone). The screen involved a 6-hour exposure to test and control materials, followed by an evaluation for erythema and edema at 24 and 48 hours post-treatment. No irritation was observed in either animal at sites with any treatment. In the main study, the 10 animals in each test group were exposed to the solid (1 cm^2), or extracts (SCI and acetone, 100%, 0.5 ml under a 25 mm Hilltop chamber). All animals were wrapped with occlusive dressings for 6 hours, once per week, during the 3-week induction phase. Scores were determined as in the screening test. Fourteen days after the final induction, the test animals were challenged with the same treatments as during the induction phase for 6 hours at naïve sites. Five animals were employed in the control group. Each of the control animals were induced with acetone alone, then challenged with the test article (solid), SCI extract (100%), and

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acetone extract (100%) in a similar manner. In addition, a positive control study was conducted to validate the sensitivity of the test system and alpha-hexylcinnamaldehyde (50% and 3% in PEG 300, respectively, for the induction and challenge phases) was selected as the positive control material. Dermal observations for sensitization were recorded at approximately 24 and 48 hours after challenge patch application. There were no scores noted for any of the test animals. There were no deaths during the course of the study. No skin effect was observed in the control animals treated with acetone only or in the animals of the test groups treated with either, solid test item, saline or acetone extract during the 3-week induction phase and at challenge. The positive and negative controls performed as expected. Under the conditions of this study, the test article and its extracts in saline or acetone did not exhibit the potential to produce dermal sensitization in guinea pigs (1).

<u>Biocompatibility</u>

Cell Culture. The cytotoxic effects of the cured test article were determined with cells in culture. Duplicate 1 cm^2 samples of test article were each placed in a cell culture well containing MRC-5, human embryonic lung cells. The test article was placed in direct contact with the cell monolayer and incubated on the cultures for approximately 24 hours at 37°C. Separate samples of the test article were extracted for 24 hours at 37°C at a surface area to volume ratio of 4.5 cm^2 per milliliter of Minimal Essential Medium. To test the extract, the growth medium was removed from the cultures and replaced with an extract; the cells were then incubated for approximately 48 hours at 37°C. A positive control for the direct cell contact and extracts (reference standard of the British Standards Institute) and a negative control (SRM-C, a high density polyethylene) were employed in the test system in the same manner. After incubation, the cells received a morphological evaluation using a light microscope. In addition, the cells exposed to the extract were tested for their ability to take up a vital dye, Neutral Red. Sodium lauryl sulfate served as the positive control for cell viability testing. No morphologic reactions were observed in either the direct contact- or extract-exposed test wells. The EC_{50}[1] of the test article could not be determined, as viability quantitated with Neutral Red was not reduced regardless of the extract concentration (5, 50 or 100%). The test article passed both the direct contact and extract assays. Therefore, it was concluded that cured test article was not cytotoxic (2).

Two additional studies were conducted. In 1 study, no cytopathic effects were reported for the test substance, saline solution extract, MEM extract, or 2 of the 3 cottonseed oil extracts. A cytopathic effect was observed for the other cottonseed oil extract, but this effect was attributed to the

[1] The concentration of extract needed to affect 50% of the cells.

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extraction medium (3). In the other study, no cytopathic effects were reported for the test article or its cottonseed oil extracts (4).

USP Class V. The ability of the material to elicit an intracutaneous or systemic response according to the USP Class V procedure was determined in rabbits and mice, respectively. The extracts of the test article were prepared at a ratio of 3 cm^2 per ml (test article to volume of vehicle) with 0.9% Sodium Chloride for Injection (SCI), 5% Ethanol in SCI (EtOH/SCI), Cottonseed Oil (CSO), and Polyethylene Glycol 400 (PEG-400) by heating at approximately 121°C for approximately 60 minutes in an autoclave. Blanks of each vehicle without test article were also extracted concurrently.

Intracutaneous Test. Six New Zealand White rabbits were divided into 2 test groups of 3 animals each. PEG extracts were diluted with SCI to 200 mg/ml for this test. All the animals in each group received 5 sequential 0.2 ml intracutaneous injections of 2 of the 4 sample extracts and their corresponding solvents, such that each extract was injected into 3 rabbits. Injections were done into back skin, on either side of the spinal column, at least 1" apart. The irritation response at each injected site was recorded at approximately 24, 48, and 72 hours after injection and compared to the score for the vehicle control. The Primary Irritation Index (PII) was 0.00, -0.07, 0.01, and 0.00 for SCI, SCO, PEG, and EtOH/SCI, respectively. These responses are classified as negligible. The intracutaneous injections of test article extracts in rabbits were no more irritating than controls for any solvent (5).

Systemic Toxicity Test. Four groups of 5 male mice were injected intravenously and 4 groups of 5 were intraperitoneally with extracts and blanks prepared in the solvents described above. Test article extracts and solvent blanks of PEG-400 were adjusted to 200 mg/ml whereas extracts and solvent blanks of other vehicles were used undiluted. The mice were observed for signs of toxicity immediately and at approximately 4, 24, 48, and 72 hours after injection. Body weights were taken before dosing and at approximately 24, 48 and 72 hours after injection. Slight weight losses (< 1.0 gram) were observed in 3 animals at 24 hours post-treatment (1 each from the Ethanol/SCI extract, Ethanol/SCI control, and CSO control groups). Slight weight losses (<1.0 gram) were also observed in 2 animals at 72 hours post-treatment (1 each from the SCI control, and PEG-400 control groups). None of these weight losses was considered noteworthy. Approximately 4 hours after dosing, 2 animals intraperitoneally injected with cottonseed oil control were observed to have wet fur in the urogenital region. The remaining animals did not exhibit any signs of acute systemic toxicity on Day 1, and no signs of systemic toxicity were noted at other observation points. Under the conditions of the study, none of the animals treated with the extracts of the test articles showed

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a biological reaction significantly greater than the animals treated with the solvent blanks. In addition, other acceptance criteria (body weight change, mortality, behavior change) for the test were met.

Based on these results, the test article was considered to have met the requirements of the USP Class V Biological Reactivity Test (6).

Another study was conducted with the test article. The extracts were injected intravenously and intraperitoneally into adult male albino mice. The mice were observed for abnormal clinical signs and for changes in weight during a 72-hour observation period. Each extract was also intracutaneously injected into rabbits. Dermal reaction in the rabbits was evaluated at approximately 24, 48, and 72 hours after injection. The saline, saline/ethanol and PEG 400 extracts resulted in no reaction when injected into mice and rabbits. The cottonseed oil extracts and controls resulted in an oily coat in the mice and very slight erythema and edema in rabbits. Based on these results, the test article was considered to have passed the USP Class V Extraction test (7).

30-Day Implant. The test article was implanted into 2 groups of 3 New Zealand White rabbits, in the paravertebral muscles and abdominal subcutaneous tissues for periods of 7 and 30 days. The negative control material, USP Polyethylene Negative Control Plastic, was implanted in the same manner into corresponding sites on the opposite sides of each animal. The test article was received sterile in the form of rods 1 mm in diameter and 15 mm in length. The negative control article was prepared in the same manner. Three rabbits were sacrificed for necropsy at 7 and 30 days post-implantation. The gross necropsy included observations of the thoracic and abdominal viscera and the collection and/or fixation of specific tissues for histological examination as needed. The implant sites were evaluated for infection, discoloration, necrosis, hemorrhage, and fibrous capsule formation. No remarkable test article-related findings were observed at any of the implant sites in any animal at either time point. In addition, the implantation sites were evaluated microscopically. The histopathology findings were 100% peer reviewed. All findings and conclusions represented a consensus between the study and peer review pathologist. After either 7 or 30 days of implantation, microscopically examination of the implants and surrounding tissue showed that the reaction to the test article was similar to the reaction to the control article. Under the conditions of this study, the local tissue reaction elicited by the implantation of the test article was similar to the control article; therefore, the test article met the requirements of the Short-term Implant Test in rabbits (8).

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