Summary of Health Data for
DOW CORNING™ MDX4-4159 50% Medical Grade Dispersion

SUMMARY

DOW CORNING™ MDX4-4159 was tested for intraperitoneal effects, skin sensitization potential, cell cytotoxicity, genetic toxicity, the presence of pyrogens, effects resulting from injection of extracts, thrombogenic and hemolytic potential, and the effects upon implantation. The material produced an LD_{50} of 1.18 g/kg upon intraperitoneal injection. When the material was coated onto Teflon® or stainless steel, neither the coated material, nor their extracts exhibited skin sensitizing potential in the guinea pig greater than control materials. The material did not exhibit any genetic toxicity in an Ames assay. Extracts of the material coated onto stainless steel were not genotoxic in a similar assay. Materials coated with MDX4-4159 did not produce cytopathic effects, nor did extracts prepared from those materials. The material did not exhibit evidence of the presence of pyrogens when coated onto Teflon or stainless steel. USP Class V extraction and testing did not produce any responses that were significantly different from solvent controls. Coated materials exhibited greater thrombogenic potential in one test, but in subsequent tests did not produce effects greater than controls. The materials coated with MDX4-4159 were not significantly hemolytic. Upon implantation, Teflon coated with MDX4-4159 produced greater reactions, at intramuscular sites, than did USP Polyethylene controls in two of three tests. In a fourth implantation test, Teflon alone elicited a greater response than did an MDX4-4159 coated Teflon. When coated onto stainless steel, the material produced equivalent reactions to stainless steel alone and to USP Polyethylene controls.

TOXICOLOGY DATA

Sensitization

Skin. Teflon® pieces one centimeter square were dip-coated in a solution of 5% MDX4-4159 and hexane. This material was tested directly or had saline extracts tested. Saline extracts were prepared by incubating 6 cm^2/ml at 120°C and 15 psi for 60 minutes. One cm^2 of solid test material or 0.1 ml of extract was applied to the backs of 10 male guinea pigs in two groups, respectively, 4 times over a period of 10 days. All animals were injected intradermally with 0.2 ml of Freunds Complete Adjuvant at the time of the third application. All exposure sites were examined for erythema or edema 48 hours after each application. After a 10-day rest period, each group received an additional application of the same test material. All animals were evaluated at 24, 48, and 72 hours after the final application for evidence of reaction. No erythema or edema was observed in animals treated with the test substance or its saline extract, nor were there differences between the weight gains of the test and control animals (1).

In a second study, MDX4-4159 was coated onto stainless steel prior to being tested for skin sensitization in direct contact or through extracts on guinea pigs. A stainless steel negative control was tested in a similar manner, and 1-chloro-2, 4-dinitrobenzene was tested as a positive control. Commercially prepared saline and 80% ethanol were used as extractants. The extracts were prepared within 24 hours of each exposure by extracting 3 cm^2 of material per milliliter of extractant. Saline extracts were prepared by autoclaving the material in extractant for 60 minutes at 121.5°C, and ethanol extracts were prepared by heating the material in extractant in an oven at temperatures ranging from 67.37 to 77.21°C for approximately 24 hours. Animals were exposed as described above. The test material when applied directly or as a saline extract did not elicit any reactions different from the stainless steel control at any time during the study. The extracts prepared in ethanol, however resulted in very slight erythema in two of the five animals tested during the challenge phase (period following exposure after a ten day rest period). Four of five animals treated with an ethanol blank exhibited very slight to well-defined

erythema reactions during the challenge phase. Under the conditions of this study, MDX4-4159 was not considered to have skin sensitizing potential in guinea pigs (2).

Genetic Toxicity

In vitro. An Ames reverse mutation assay was performed using DOW CORNING™ MDX4-4159. *Salmonella typhimurium* of various strains were exposed to the test material in the presence or absence of an enzyme activating system. The test material did not demonstrate genetic activity in any test (3).

MDX4-4159 was coated onto stainless steel and extracted in saline and acetone prior to testing in a Bacterial Reverse Mutation Assay. The extracts were prepared by gently shaking 6 cm^2 of material per milliliter of each extractant at 37°C for 24 hours. The tester strains used in the assay were *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* strain WP2*uvr*A^-. The strains were incubated in both the presence and absence of Aroclor induced rat liver S9. No strains exhibited increases in the number of revertants with either extract, with or without S9. The extracts gave no indication of genetic activity in this assay (4).

Biocompatibility

Cell Culture. Filter pads dipped in hexane solutions of 0.05%, 0.5%, and 5% MDX4-4159 and allowed to air dry produced no changes in cell morphology after direct contact with cell monolayers for 24 hours at 37°C. After the incubation, the cell cultures were examined microscopically and their results compared to the results from positive and negative control cultures. No cytopathic effect was observed for the test materials (5).

In a second study of cytotoxicity, 5% MDX4-4159 in hexane was used to dip-coat one-centimeter square pieces of Teflon or polyethylene. Filter pads dipped in hexane solutions of 0.05%, 0.5%, 5%, and 50% MDX4-4159 were also tested in cell culture. After at least 24 hours of air cure, these materials were placed in direct contact with a confluent monolayer of human embryonic lung cells and incubated for 24 hours. The only difference from control cultures was observed with a pad dipped in 50% fluid in hexane, which elicited a slight cytopathic response (6).

A test of the cytotoxicity of MDX4-4159 was performed with the material coated onto stainless steel. The coated steel was placed in direct contact with human embryonic lung cells (MRC-5) in culture for 24 hours. The coated stainless steel was also extracted in Minimal Essential Medium (MEM) at 37°C for 24 hours and the extract tested with the same cells in culture for 48 hours; the extract was tested at concentrations of 100%, 50%, and 5%. After the incubation periods, the cells were examined microscopically and by uptake of vital dye (neutral red). None of the measures indicated cytotoxicity of the MDX4-4159 coated stainless steel or its extracts. The material was considered to have passed the cytotoxicity test (7).

The cytotoxic potential of MDX4-4159 on Stainless Steel, Cured was assessed by means of the colony forming ability test using the Chinese hamster fibroblast cell line V79. The study was conducted according to the following guidelines: ISO 10993-5, 2009 (Tests for cytotoxicity: In vitro methods, 2009) & Part 12 (Sample preparation and reference materials, 2007), YAKUSHINATSU No. 0213001, February 13 2003 and PFSB-Medical Device No. 0428001 April 28, 2005. MDX4-4159 50% on Stainless Steel, Cured, reference item Type 316 stainless Steel Shim Stock Sheet, 0.015 inch thick (Item Number 231K19) and positive & negative controls were extracted for 24 hours in cell culture medium MEM at 37 ± 1.5 °C. The test and the reference items were extracted at a surface area to volume ratio of 5 cm^2/ml while the positive and negative controls were extracted at a surface ratio to volume ratio of 6 cm^2/ml. The cells were incubated for 6 days with the different extracts and their dilutions as

follows: MDX4-4159 50% Medical Grade Dispersion on Stainless Steel, Cured and Type 316 stainless Steel Shim Stock Sheet, 0.015 inch thick (Item Number 231K19)) - 3.125%, 6.25, 12.5%, 25%, 50%, and 100% (v/v), positive control (RM-A) - 1%, 25%, 50%, and 100% (v/v), positive control (RM-B) - 1%, 25%, 50%, and 100% (v/v). No relevant difference between the medium control (culture medium) and the negative control (eluated RM-C) was observed. The positive control RM-A had an IC50 value less than 7% and the positive control RM-B had an IC50 value less than 70%. These results met the acceptance criteria. Cytotoxic effects were not observed following incubation with extracts of MDX4-4159 on Stainless Steel, Cured at all tested concentrations, as well as with extracts of the reference item Type 316 stainless Steel Shim Stock Sheet, 0.015 inch thick (Item Number 231K19). Due to the lack of cytotoxicty no IC50 value could be calculated. Under the experimental conditions reported, cell culture medium extracts of MDX4-4159 on Stainless Steel, Cured do not possess a cytotoxic potential (8).

Pyrogen. Saline extracts of MDX4-4159-coated Teflon were prepared by autoclaving 3 cm^2/ml at 120°C and 15 psi for 50 minutes. The cooled extracts were injected into the marginal ear veins of five rabbits at a dose level of 10 ml/kg. Rectal temperatures were monitored over a three-hour period. None of the animals showed an individual temperature increase of 0.6°C or more above control temperatures. Further, the sum of the three greatest temperature increases did not exceed 1.4°C (9).

In a second study, MDX4-4159 was coated onto stainless steel, and 6 cm^2 per ml of saline was extracted at 121°C for 60 minutes. The saline extract was injected into each of three rabbits at a dose of 10.0 ml/kg. Rectal temperatures of the rabbits were recorded prior to dosing, and at 1.0, 1.5, 2.0, 2.5, and 3.0 hours after dosing. One animal did not have a rise in temperature, one animal had a maximum temperature rise of 0.08°C, and the third animal had a maximum temperature rise of 0.32°C. The sum of the maximum temperature increases was 0.40°C. The saline extracts of MDX4-4159 coated stainless steel were not pyrogenic in the rabbit (10).

USP Class V. Teflon dipped into a solution of 5% MDX4-4159 in hexane was extracted in saline, saline/ethanol, polyethylene glycol 400 (PEG 400), or cottonseed oil at a surface area to volume ratio of 3 cm^2/ml. Two groups of 5 male Swiss Webster mice received intravenous injections of saline or saline/ethanol. Two separate groups of 5 male Swiss Webster mice received intraperitoneal injections of the PEG 400 or cottonseed oil extracts. The animals were observed for 24, 48, and 72 hours after injection. Further, rabbits received intracutaneous injection of each extract and were observed at 24, 48, and 72 hours after injection. No differences in behavior were noted in the mice receiving the extracts compared to controls, nor were differences observed in the rabbits receiving the extracts (11).

In a second study, saline, saline/ethanol, polyethylene glycol (PEG) 400, and cottonseed oil extracts of the elastomer were prepared using 6 square centimeters of the test material per ml of an extractant. Fifty ml extract/kg, or 8 g/kg in the case of PEG 400, was administered to groups of 5 male Swiss Webster mice via intravenous (saline, saline/ethanol extracts) or intraperitoneal injections (PEG 400, cottonseed oil extracts). Additionally, 0.2 ml/site of each extract are intradermally administered into 10 sites on groups of 2 male New Zealand White rabbits. No adverse effects in any parameter evaluated were observed following either of the Class V Extractables Tests for any of the extracts tested (12)

In another study, MDX4-4159 was coated onto stainless steel and was extracted at a ratio of 6 cm^2 of coated stainless steel per milliliter to saline, saline/ethanol, polyethylene glycol 400 (PEG 400), or cottonseed oil at a surface area to volume ratio of 6 cm^2/ml. The material in each of the extractants used above was autoclaved at 120.5 to 121.5°C for 60 minutes. Corresponding blanks were similarly prepared. The extracts were injected into CD-1 mice and New Zealand White rabbits as described above. Two mice of the PEG 400 blank were found dead, so two additional mice were injected with the blank. The mice receiving the PEG 400 blank generally behaved abnormally, therefore, twenty

additional mice (ten received the blank and ten received the extract) were injected with a freshly prepared extract or blank. No abnormal behavior was otherwise noted in the animals compared to the controls. The rabbits receiving the saline, saline/ethanol, or PEG 400 extracts, or the respective blanks did not exhibit dermal reactions. Only very slight erythema reaction was observed at one injection site treated with the cottonseed oil blank, and no reactions were noted with the extract. MDX4-4159 was considered to have passed the USP Class V test (13).

Thrombogenicity. A 5% solution of MDX4-4159 was used to coat Teflon. The coated Teflon was then tested in a Closed Cell Blood Coagulation Test using fresh uncoagulated canine blood. There was no difference between the test and control materials; however, since the standard deviation of the mean for the test material was greater than 0.4, a retest was performed. In the retest, the test material showed a significantly greater thrombogenic potential than the control material (14).

In a second test, a similarly prepared material was tested twice and found not to have significantly different thrombogenic potential compared to the control material. The second test resulted in a standard deviation of the mean, which was greater than 0.4, indicating another retest was necessary, but the material's shelf life precluded performing another test (15).

Hemolysis. Teflon FEP dip-coated in a 5% solution of MDX4-4159 in hexane was tested directly or extracted in physiological saline at 3 cm^2/ml, 121°C and 15 psi for 60 minutes. Fresh anticoagulated blood from New Zealand White rabbits was placed in direct contact with the test substance or saline extract and incubated at 37°C for 4 hours. Following incubation, the samples were analyzed for free hemoglobin by spectrophotometry to determine hemolytic potential. Neither the test material nor the extract produced hemolysis greater than that produced by the control material (16).

A test of the hemolytic potential of MDX4-4159 was performed with the material coated onto stainless steel. The coated steel was placed in direct contact with rabbit blood (3 cm^2/ml) for one hour under dynamic conditions. The coated stainless steel was also extracted in 0.9% sodium chloride for injection by autoclaving at 121°C for one hour and the extract tested with the blood for one hour under dynamic conditions. Untreated stainless steel served as a control. After the incubation periods, the blood was centrifuged and the optical density at 545 nm was determined for the supernatants. Neither MDX4-4159 stainless steel nor its extracts were hemolytic (17).

Ninety-day Implant. MDX4-4159 coated Teflon was implanted into 4 intramuscular and 2 subcutaneous sites in each of 12 rabbits. Each rabbit received equal numbers and types of implants of USP negative control plastic. The animals were observed daily for survival and overt signs of toxicity and were weighed prior to study initiation and at terminal sacrifice. Groups of 3 animals were sacrificed at 3, 10, 30, and 90 days after the implantation of the test and control materials, and the implantation sites examined grossly and microscopically. Selected organs and tissues were also examined histopathologically. Encapsulation was reported at more sites than control siltes at 3 and 90 days after implantation, though there were no significant differences at 10 and 30 days after implantation. At 3 days after implantation, hemorrhaging was reported around both the test material and control material sites, while at 10 days after implantation, more hemorrhaging was noted at the test material sites than at the control sites. No hemorrhaging was noted at 30 and 90 days after implantation. No treatment related changes were reported in the organs examined histopathologically (18).

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microscopically. Selected organs and tissues were also examined histopathologically. No significant differences were noted between the test and control implant sites and no histopathological changes were reported for any of the organs examined (19).

MDX4-4159 coated Teflon was implanted into 4 intramuscular and 2 subcutaneous sites in each of 9 rabbits. Each rabbit received equal numbers and types of implants of USP negative control plastic. The animals were observed daily for survival and overt signs of toxicity and were weighed prior to study initiation and at terminal sacrifice. Groups of 3 animals were sacrificed at 10, 30, and 90 days after the implantation of the test and control materials, and the implantation sites examined grossly and microscopically. Selected organs and tissues were also examined histopathologically. Gross response to the test and control materials was comparable in type and severity at the 10 and 90 day periods. However, at the 30 day sacrifice, more connective tissue was observed at intramuscular sites of MDX4-4159 compared to the control sites. At 30 and 90 days, tissue response to MDX4-4159 was greater than the response to the control material at nearly all sites. Due to these findings, MDX4-4159 did not pass this 90-day implantation test (20).

In another implant test with a protocol similar to the above, Teflon strips were compared to MDX4-4159-coated Teflon. No consistent differences were noted between macroscopic responses to test and control implants at any site over any sacrifice interval. Microscopic tissue response 10 days post-implantation was less than at 30 days. At both time periods, control Teflon appeared to elicit a slightly greater (but not significant) fibroblastic reaction than did the silicone-coated Teflon strips. By 91 days post- implantation, tissue responses were essentially the same for both materials. Microscopic evaluations of selected organs retrieved at 10 and 90 days revealed no unusual abnormalities (21).

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