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TOXICITY STUDIES OF COOLANOL® 15

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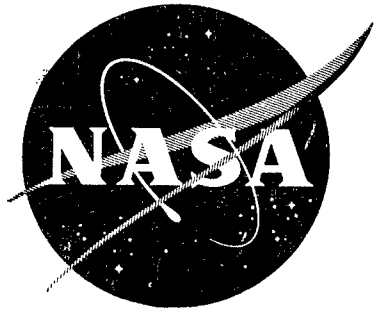

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Foreword

This work was performed under Project 6302 "Toxic Hazards of Propellants and Materials," Tasks 630201 "Toxicology" and 630206 "Toxicological Support," at the request of the Manned Spacecraft Center, National Aeronautics and Space Administration, Houston, Texas under NASA-MSC Contract T-31248-G. Dr. Elliott Harris served as contract monitor for NASA-MSC and Dr. Kenneth C. Back as technical consultant for the Aerospace Medical Research Laboratories. The work was initiated in January 1965 and completed in September 1965 in the Toxic Hazards Branch, Physiology Division, Biomedical Laboratory. The assistance rendered by members of the Veterinary Medicine Division, Aerospace Medical Research Laboratories is gratefully acknowledged.

This technical report has been reviewed and is approved.

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Abstract

Coolanol® 15 (formerly designated MCS 198), a synthetic heat transfer fluid, is currently being used in the heat transfer systems of manned spacecraft. The current studies were undertaken to confirm or refute previously reported effects on the central nervous system and to acquire additional information on the toxicity of this compound. The effects of single intraperitoneal injections in mice and rats, repeated subcutaneous injections in rabbits, and the repeated cutaneous application on the unabraded skin of rabbits, monkeys, and dogs were investigated. Parenteral injection revealed that Coolanol 15 is relatively nontoxic. The LD_{50} for mice was found to be greater than 20.0 gm (22.2 ml) per kg at 24 hours and 5.9 gm (6.6 ml) per kg at 7 and 14 days. Repeated subcutaneous injections in rabbits resulted primarily in localized reactions at injection sites. The only effects which could be directly attributed to the cutaneous application of 3.6 gm (4.0 ml) per kg per day for 20 days involved the skin. Drying and encrustation and/or desquamation of the superficial layers of the skin were the principal lesions observed clinically, while microscopic examination revealed varying degrees of hyperkeratosis and cellular infiltration. These studies failed to confirm the previously reported lesions in the central nervous system attributed to Coolanol 15.

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SECTION I

Introduction

Coolanol® 15 (formerly designated MCS 198), a synthetic heat-transfer fluid developed by the Monsanto Company, St. Louis, Missouri, is currently being used in the heat transfer systems of manned spacecraft. Since astronauts could be exposed to the fluid if equipment failure resulted in its release into the air-conditioning system of the cabin or space suits, a knowledge of the toxicity of the compound is of vital importance. Unpublished data received by the National Aeronautics and Space Administration revealed focal changes in the central nervous system of rabbits that received cutaneous applications of 1.5 and 2.5 ml/kg daily for 20 days. These changes consisted of nodular glial and ependymal proliferations, pigment deposits and perivascular lymphocytic infiltration, and were believed to be related to the Coolanol 15. Lesions were not observed, however, in animals that had received daily applications of 4.0 ml/kg.

In this investigation, acute and subacute parenteral administration studies and a subacute cutaneous application study were completed in several species of animals. These were undertaken to confirm or refute the previously reported effects on the central nervous system and to acquire additional information on the toxic properties of this compound.

SECTION II

Acute Toxicity

METHOD

Male Swiss mice weighing between 15.5 and 27.5 grams were given Coolanol 15 by intraperitoneal injection at dose levels varying between 2.5 and 20.0 gm/kg (2.8 to 22.2 ml/kg). In addition, a preliminary screening of the dose response was accomplished in male Sprague-Dawley strain rats weighing between 160 and 255 grams. During the course of the study, the animals were individually housed in hanging wire mesh cages. Rockland Mouse/Rat Diet and tap water were available ad libitum.

RESULTS

MICE

The ratios of deaths to number of animals injected were as follows:

	Dose – gm/kg						
Time Observed	*2.5*	*3.5*	*5.0*	*5.7*	*7.1*	*10.0*	*20.0*
24 hours	0/5	1/25	0/30	0/15	0/25	0/5	0/5
7 days	0/5	4/25	8/30	7/15	16/25	5/5	4/5
14 days	—	4/25	8/25	7/15	17/25	—	—

The following LD_{50} values and slope functions and their respective 95% confidence intervals were determined using the method of Litchfield and Wilcoxon*.

Time	*LD_{50}*	*Slope Function*
24 hours	>20.0 gm/kg	—
7 days	5.90 gm/kg (5.09 - 6.84)	1.67 (1.40 - 1.99)
14 days	5.90 gm/kg (5.00 - 6.96)	1.62 (1.15 - 2.28)

Clinical observations included some reduction in activity following injection, loose stools, anorexia, slight hyperexcitability when disturbed, slight ocular discharge, and some degree of photophobia. Improvement was observed in 3 to 6 days in affected animals that lived.

Necropsies were performed on five mice that died between 72 and 120 hours postinjection at doses ranging from 3.5 to 7.07 gm/kg. All exhibited generalized autolytic changes which complicated the examination. In general, however, there was congestion, edema or hemorrhage, and cellular infiltration in the lungs. Granular cast formation and degenerative tubular changes were seen in the kidneys. One animal had a small glial focus in the cerebral cortex. This was probably due to an infection by *Encephalitozoon* sp. or similar organism and not related to the Coolanol 15 injection.

* Litchfield, J. T., Jr. and F. Wilcoxon, "A Simple Method of Evaluating Dose-Effect Experiments," *J. Pharmacol. Exptl. Therap.*, 96: 99-113, 1949.

RATS

The ratios of deaths to number of animals injected were as follows:

Time Observed	*Dose – gm/kg* 2.5	5.0	10.0	20.0
24 hours	0/5	0/5	0/5	0/4
7 days	0/5	0/5	5/5	4/4

Clinical observations were similar to those seen in mice but also included a nasal discharge. A moderate weight loss was noted in animals that survived.

Necropsies were performed on three animals that died and one animal that was killed in a terminal state between 3 and 11 days postinjection. Lesions observed included marked generalized peritonitis, toxic tubular nephritis, and congestion of the liver with inward extension of perihepatitis. Spontaneous lesions not related to the Coolanol 15 injection included bilateral otitis media and mild chronic murine pneumonia. One animal that exhibited symptoms of a central nervous system disturbance before death had mild lymphocytic infiltrations and scant hemorrhage in the leptomeninges and focal hemorrhagic encephalomalacia in the temporal cortex which appeared to be of infectious etiology.

SECTION III

Subacute Toxicity

METHOD

Two albino rabbits each weighing 2.0 kg, were given subcutaneous injections of Coolanol 15 for 14 days. Two-day intervals separated injection periods of 5, 5, and 4 days. Eight injection sites, four on each side, located lateral to the dorsal midline were used. A dose of 270 mg (0.30 ml) per kg was given daily for the first 5-day period. This was increased to 540 mg (0.6 ml) per kg during the remaining periods. The two treated animals and one control animal that had been given saline were killed by an intravenous injection of pentobarbital sodium on the fourth day following the last injection. The animals were housed in individual cages and given Purina Rabbit Chow and tap water ad libitum during the course of the study.

RESULTS

Significant clinical manifestations were limited to local reactions at the injection sites. These ranged from little or no reaction to erythema, edema, induration, and abscess formation. Only mild reactions were observed when the Coolanol 15 dispersed rapidly. The inconsistent response at injection sites apparently resulted from differences in the subcutaneous tissue plane in which the liquid was deposited.

The Coolanol 15 used for injection was bacteriologically negative when cultured in thioglycollate broth and on blood agar and EMB plates.

The principal lesions observed at necropsy were multiple subcutaneous abscesses at injection sites in the animals that received Coolanol 15. Bacteriologic cultures of abscess contents were negative. Both rabbits had scattered foci of purulent pneumonia, and mild inflammatory foci were present in the portal areas of the liver. A section of the thoracic spinal cord from one animal revealed an organizing cellular mass in the central canal which did not appear to be the result of the Coolanol 15 administration. No other lesions were observed in the central nervous system of either animal.

The only lesions observed in the control animal were petechiae in the subcutaneous tissues at the injection sites and a few scattered granulomata of infectious etiology in the liver.

SECTION IV

Cutaneous Application

METHOD

Coolanol 15 was applied to the unabraded skin of four albino rabbits, four *Macaca mulatta* monkeys, and four mongrel dogs. Applications were made 5 days per week for 4 weeks, making a total of 20 days of application. The amount of Coolanol 15 applied was 4.0 ml/kg body weight per day with the volume adjusted to the body weight at the beginning of each weekly application period. The daily dose was divided into 4 separate applications of 1.0 ml/kg each which were applied at approximately 0830, 0930, 1430, and 1530 hours. This was done in an attempt to limit the application area to about 10% of the total body surface and was based on the results of preliminary trials on rabbits with dye added to the compound. Distilled water was applied to two control animals of each species. Glass syringes with blunted 20-gauge needles were used to spray the Coolanol 15 or distilled water on the skin surface. Application was made along the dorsal midline from about midscapula to the sacral area. The monkeys were held in a horizontal position during the application. From 10 to 15 minutes were required to treat all 18 experimental and control animals.

The backs and sides of all animals were clipped before the first application of Coolanol 15. Due to the rapid spread of the compound, the chest and abdomen of the monkeys were also clipped at the beginning of the second weekly application period. All animals were reclipped as necessary at the time body weights were obtained each week.

Body weights were obtained by having a caretaker hold the animals while standing on a physician's office scale and subtracting the caretaker's weight from the gross weight obtained.

The animals were housed in individual cages during the course of the study. Water was available ad libitum. Dogs were fed Teklad Dog Diet with cooked or canned horsemeat twice daily, monkeys were given Purina Monkey Chow twice daily supplemented with fruit or vegetables in the afternoon, and rabbits had Purina Rabbit Chow available ad libitum.

On the third day following the final application, all surviving animals were killed with an overdose of pentobarbital sodium administered intravenously and necropsies were performed.

At necropsy, gross observations were recorded and tissues from the major organ systems were fixed in buffered formalin for subsequent microscopic examination. In addition, skin specimens from the shoulder, dorsal thoracic and lumbar areas, and flank were obtained and marked for identification. The entire brain and portions of the cervical, thoracic and lumbar spinal cord were also saved for examination. The brain was sliced grossly at 0.5 to 1.0 cm intervals. Portions of alternate slices of the brain and all other tissues were processed and stained with hematoxylin and eosin. In addition, selected sections from four areas of the brain and the thoracic and lumbar spinal cord of selected animals were stained with Luxol Fast Blue-cresyl violet. Frozen sections of two areas of the brain and the cervical spinal cord were prepared from fixed tissue from the same animals. These were stained by Cajal's gold sublimate method for the demonstration of astrocytes.

RESULTS

The Coolanol 15 spread rapidly over the skin surface even when applied in a narrow band along the dorsal midline. The rapidity and extent of the spread on monkeys and dogs was con-

siderably greater than anticipated. By the time the monkeys were returned to the cage, the Coolanol 15 had generally spread completely around the body. There was some spread down the legs if the animal was held in a vertical position after application or stood in an upright position when returned to its cage. The second application in the morning or afternoon frequently spread to the ventral midline of dogs within 15 minutes. On the rabbits, the Coolanol 15 rarely spread beyond the clipped area which involved approximately 15% of the body surface. Skin lesions which developed, particularly on the rabbits, inhibited the spread.

Some licking of the skin surface occurred following the application of Coolanol 15. This was observed most frequently in the rabbits and occasionally in the dogs.

There apparently was some irritative sensation immediately after the application of Coolanol 15. This was most pronounced after the appearance of skin lesions. Beginning with the second weekly application period, rabbits made definite efforts to escape from restraint while the substance was being applied or immediately after application. This was also seen in monkeys and dogs to some degree although the relationship between skin lesions and escape reaction was less definite.

The following body weight data were obtained during the study:

		Body Weight – kg				
Animal	*Sex*	*8 Mar(a)*	*15 Mar*	*22 Mar*	*29 Mar*	*5 Apr(b)*
Rabbits						
A16	M	2.0	2.0	1.8	(d)	–
A18	M	1.9	2.0	1.7	1.8	1.7
A20	M	2.0	2.6	2.4	2.3	2.2
A24	M	2.5	2.5	2.3	2.5	2.5
A14(c)	M	2.4	2.5	2.6	2.5	2.6
A26(c)	M	2.0	2.5	2.4	2.6	2.8
Monkeys						
A31	F	2.3	2.2	2.1	2.3	2.2
A33	F	2.2	2.4	2.3	2.3	2.0
A43	F	2.4	2.4	2.3	2.0	2.0
A45	F	2.5	2.4	2.5	2.5	2.2
A37(c)	F	1.9	2.2	1.9	2.0	2.0
A47(c)	F	2.4	2.3	2.3	2.3	2.3
Dogs						
B31	F	6.4	6.5	6.1	7.0	6.4
B61	F	11.4	10.9	10.7	11.4	10.7
C60	M	9.1	8.6	8.5	9.0	8.4
C84	M	9.5	10.0	9.3	9.5	8.9
B13(c)	F	9.1	9.9	9.3	9.5	8.8
C82(c)	M	9.5	10.0	10.0	9.9	10.0

(a) date of first application
(b) date of necropsy
(c) control animals
(d) died 28 Mar – weight at necropsy on 29 Mar was 1.5 kg

CLINICAL OBSERVATIONS

RABBITS

One rabbit, A16, died during the course of the study. The animal was found dead in its cage on the second day following the completion of the third weekly application period. This animal had shown a poor appetite and marked loss of body weight for about a week before death.

The skin lesions which developed on the back and sides as the result of Coolanol 15 application were similar in all animals, although there was some variation in the time of appearance. Some clinical improvement was generally noted over the weekends when no applications were made.

Early in the study, a mild erythema was observed in the area of application in the afternoons. By the end of the first week, all animals exhibited a dry, cracking skin. During the second week there was an increase in dryness and cracking and a thick white encrustation developed. In several unclipped areas where the Coolanol 15 had spread, exudation also resulted in scab formation.

At the end of the second week, the heavy white crust began to slough, exposing a thinly keratinized pliable surface with red lines where major cracks were present. The area gradually assumed a dry scaly appearance and by the end of the study, the skin had become somewhat thickened and again covered with a cracked white encrustation similar to that seen earlier. Early hair growth in the area of application was rather sparse, but by the end of the study, the three remaining animals had a dense hair growth.

No lesions were observed on the two control animals.

MONKEYS

The response in monkeys to the cutaneous application of Coolanol 15 was less severe than that seen in rabbits. Three of the four monkeys exhibited minimal erythema and developed scurfy (dandruff-like) skin lesions that persisted throughout the study. At necropsy, the skin was dry, moderately scurfy, and areas of superficial desquamation were present. Areas of skin to skin contact, such as the inguinal and axillary regions, were most severely affected. In general, there was also partial loss of hair on the extremities, and one animal exhibited localized alopecia of the head.

One monkey, A43, was more severely affected. In addition to the scurfy skin, exudation and encrustation were observed in the inguinal and axillary regions at the end of the first week. These lesions extended over the entire trunk during the second week and resulted in some cracking of the skin and scab formation. During this period, the animal's activity and appetite were somewhat depressed. Moderate improvement was observed during the third week, although the skin appeared somewhat hyperkeratotic. At necropsy, the skin on the back of the animal was dry, wrinkled, and scurfy. Considerable desquamation and apparent mild exudation were observed on the chest, abdomen, and inguinal and axillary regions.

No lesions were observed on the control animals.

DOGS

The severity of the reaction to Coolanol 15 was variable in dogs. Dog B31 exhibited mild erythema following application and developed a scurfy skin which progressed to slight super-

ficial desquamation by the end of the second week. Some inflammation in the flank areas was also observed. At necropsy, the back and sides of the animal were moderately scurfy.

Animal B61 was only slightly affected. Mild erythema was observed infrequently. A few papules developed on the back. At necropsy, the skin in the application area was only slightly scurfy with a few small scabs remaining in the area of the papules.

Animal C60 developed a slight flaking of the skin during the first week of application. This increased moderately during the second week and was accompanied by inflammation and scab formation in the flank region. A few papules developed, but at necropsy the skin on the body was only slightly scurfy and there was a mild inflammatory process present in the flank regions.

Dog C84 was most severely affected. During the first week the clipped area became slightly scurfy and the adjacent unclipped areas inflamed. The degree of involvement increased during the second week. Localized alopecia and desquamation were observed in the adjacent unclipped areas. The inflammatory process was most severe in the flank and axillary regions and resulted in some exudation and encrustation. By the end of the second week, desquamation had occurred over one-third of the application area. Recently desquamated areas became quite reddened when the Coolanol 15 was applied. The entire area was involved the following week and had a quite scurfy appearance. The flank and tail-base area were markedly inflamed. At the time of necropsy, desquamation was still in progress and some inflammation was observed.

Control animals showed no evidence of skin lesions at necropsy.

PATHOLOGY

RABBITS

The primary effects of Coolanol 15 applications were observed in the skin. All animals developed a moderate to marked degree of hyperkeratosis and desquamation of the stratum corneum. Lymphocytic infiltration of the dermal papillae and early suppuration and abscess formation in the follicular areas were also observed.

Kidney changes were found in three of the four animals. The animal that died had a moderate subacute infectious nephritis while the other two animals exhibited one or more of the following: focal tubular degeneration, edema of the mucosa of the renal pelvis and proximal ureter, congestion of the medulla, and necrotic material in an occasional renal tubule. The two animals that were killed at the end of the study also had areas of tubular dilatation and atrophy and old bland scar. One had multiple epithelium-lined cortical cysts. These lesions were chronic in nature and apparently existed before the study.

There was an indication of hyperchromaticity of glial cells, some satellitosis, and vacuolization of small neurons, especially in the cord sections, of the animal that died. Glial nodules were observed in the outer layer of the cerebral cortex in one of the control animals. The lesions in the control animal were compatible with an infection by *Encephalitozoon* sp. or similar organism.

Some degenerative changes were observed in the livers of three of the four treated animals, and some lymphocytic and plasma cell infiltration was observed in the livers of control animals. Focal chronic inflammatory lesions observed in the lungs and hearts of both experimental and control animals were not considered to be significant.

The death of the one animal was apparently due to a septicemic disease, possibly introduced through a skin portal secondary to drying and cracking of the integumentary barrier.

MONKEYS

Mild to moderate hyperkeratosis of the skin with some lymphocytic and plasma cell accumulations was observed in the four treated animals. One treated monkey, A43, had focal hepatocellular necrosis associated with an inflammatory response, focal pneumonitis, patchy pulmonary edema and blood in the larger bronchi. Focal inflammatory lesions in the lung, liver, and kidneys and mild hepatic cell vacuolization were not significantly different in the experimental and control groups.

No central nervous system lesions were present in either the treated or control animals.

DOGS

All animals in the treated group developed a mild hyperkeratosis. This was localized in the flank region in one of the animals. Microabscesses in the corium and subepidermal and perifollicular infiltration of inflammatory cells were observed in one of the animals, and an influx of subepidermal lymphocytic and epithelioid cells was found in the flank area of another. Hyperkeratosis was also observed in one of the control animals.

One treated animal (C84) showed focal hepatic inflammatory lesions containing polymorphonuclear and lymphocytic cells, centrilobular swelling and eosinophilia of hepatic cell cytoplasm, and mild bile stasis. These changes were suggestive of regeneration in a continuing active hepatitis. Focal inflammatory lesions were observed in the lungs and kidneys from both treated and control animals.

SECTION V

Discussion

The results of single intraperitoneal injections in mice and rats indicate that Coolanol 15 is relatively nontoxic. In those animals that received a lethal dose, death was somewhat delayed. Lesions observed indicate that the substance is rather irritating to the peritoneum. Large doses apparently have some toxic effects on the kidneys but the significance of other lesions observed was not established. Body weight loss could be attributed to the peritonitis which developed. No pathologic changes directly attributable to Coolanol 15 were observed in the central nervous system. One mouse did show a small glial focus in the cerebral cortex. Although the organism was not demonstrated, this was probably due to an infection by *Encephalitozoon* sp. or similar organism.

The results of repeated subcutaneous injections in rabbits failed to reveal a significant toxic effect. Lesions observed were primarily associated with the irritant effect at the site of injection. Although some changes were observed in sections of spinal cord from one animal, they did not appear to be the primary result of Coolanol 15 administration. The inflammatory lung and liver lesions observed have been seen frequently in rabbits from other study groups and cannot be causally related to the administration of this compound.

The primary clinical and pathologic effects of the cutaneous application were observed in the skin. Rabbits were the most severely and uniformly affected. All animals of this species developed a dry cracked skin with a heavy white encrustation which sloughed, leaving a newly keratinized surface on which an encrustation again developed after further applications of Coolanol 15. Drying and superficial flaking of the skin were the lesions most often observed in monkeys. A partial loss of hair on the extremities was also noted. One monkey did develop a generalized serous exudation and encrustation of the trunk with some cracking and scab formation. The degree of skin involvement in the dogs was also variable, ranging from mild erythema and some scurfiness to superficial desquamation over the entire dorsal and lateral surfaces of the trunk with moderate regional inflammation. The prominent histopathologic findings were hyperkeratosis, cellular infiltration in the dermal papillae, and perifollicular microabscess formation. The spontaneous hyperkeratosis observed in one of the control dogs is not considered significant since this is occasionally seen in animals of this species.

The dense hair growth observed in treated rabbits at necropsy was not apparent in control animals. The relationship between this dense hair growth and Coolanol 15 was not established since it was not confined strictly to the application area, and rabbits of the age used in this study may show rapid growth of "new hair."

Although the dog that was most severely affected was the only animal with a completely pigmented skin, there appeared to be no relationship between pigmentation and reaction to Coolanol 15. No difference was observed in the reaction of pigmented and unpigmented areas on one of the other animals.

Systemic effects were observed in only two of the treated animals. The rabbit that died exhibited a poor appetite and marked weight loss before death. Death, however, was apparently due to a septicemic disease which may possibly have been the result of the entrance of microorganisms through the dry cracked skin. The monkey that developed the most severe skin lesions

and showed visceral lesions at necropsy exhibited a transient depression in motor activity and appetite during the second week of the application period when the skin lesions were most acute. This may have been a reaction to the skin lesions or related to the pneumonitis and hepatitis seen at necropsy. The latter conditions are occasionally seen in control monkeys, and it is unlikely that they were related to the Coolanol 15 application.

The results of body weight observations are inconclusive. Although there appears to be an adverse effect on body weight, there is some inaccuracy inherent in the weighing method used.

The relationship between kidney and liver lesions observed in three of the four treated rabbits and the application of Coolanol 15 is questionable. One of the animals involved was the one that died. In addition to the acute kidney changes observed in the other two animals, chronic lesions indicative of a preexisting disease process were present.

It is unlikely that the liver lesions found in one of the treated dogs were related to the Coolanol 15. The changes were indicative of regeneration accompanying a continuing active hepatitis and were compatible with those occasionally seen in control animals from other study groups.

No central nervous system lesions which could be attributed to the cutaneous application of Coolanol 15 were observed. Lesions were demonstrated in only one of the treated animals, the rabbit that died. These were nonspecific and apparently related to a septicemic disease rather than to the application of Coolanol 15. One of the control rabbits did show glial nodules in the cerebral cortex. Although the organism was not demonstrated, these lesions were compatible with an infection by *Encephalitozoon* sp. or similar organism.

The results of these studies do not substantiate the causal relationship between Coolanol 15 and central nervous system lesions as previously reported. The failure to demonstrate lesions directly attributable to Coolanol 15 in a variety of animals by several methods of exposure indicates that the changes reported in rabbits may have been due to a spontaneous disease process, possibly an infection by *Encephalitozoon* sp.

SECTION VI

Conclusions

Parenteral injections revealed that Coolanol 15 is relatively nontoxic. The intraperitoneal LD_{50} for mice was found to be greater than 20.0 gm/kg (22.2 ml/kg) at 24 hours and 5.90 gm/kg (6.6 ml/kg) at 7 and 14 days. Repeated subcutaneous injections in rabbits resulted primarily in localized reactions at injection sites. No central nervous system lesions directly attributable to Coolanol 15 were observed.

The only effects which could be directly related to the repeated cutaneous application of Coolanol 15 involved the skin. Drying and encrustation and/or desquamation of the superficial layers of the skin were the principal lesions observed clinically while microscopic examination revealed varying degrees of hyperkeratosis and cellular infiltration. Rabbits were the most severely and uniformly affected.

Neither the death of one rabbit nor the visceral lesions observed at necropsy could be directly attributed to the cutaneous application of Coolanol 15. Body weight data were inconclusive. The only central nervous system changes observed in a treated animal were those seen in the rabbit that died and were apparently due to a septicemic disease. Glial nodules were observed, however, in one of the control rabbits.

These studies failed to substantiate the previously reported changes in the central nervous system attributed to Coolanol 15. It is possible that the lesions observed in rabbits in the previous study were due to a spontaneous infection by *Encephalitozoon* sp. or other similar organism.

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13. ABSTRACT

Coolanol® 15 (formerly designated MCS 198), a synthetic heat transfer fluid, is currently being used in the heat transfer systems of manned spacecraft. The current studies were undertaken to confirm or refute previously reported effects on the central nervous system and to acquire additional information on the toxicity of this compound. The effects of single intraperitoneal injections in mice and rats, repeated subcutaneous injections in rabbits, and the repeated cutaneous application on the unabraded skin of rabbits, monkeys, and dogs were investigated. Parenteral injection revealed that Coolanol 15 is relatively nontoxic. The LD_{50} for mice was found to be greater than 20.0 gm (22.2 ml) per kg at 24 hours and 5.9 gm (6.6 ml) per kg at 7 and 14 days. Repeated subcutaneous injections in rabbits resulted primarily in localized reactions at injection sites. The only effects which could be directly attributed to the cutaneous application of 3.6 gm (4.0 ml) per kg per day for 20 days involved the skin. Drying and encrustation and/or desquamation of the superficial layers of the skin were the principal lesions observed clinically. while microscopic examination revealed varying degrees of hyperkeratosis and cellular infiltration. These studies failed to confirm the previously reported lesions in the central nervous system attributed to Coolanol 15.

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	ROLE	WT	ROLE	WT	ROLE	WT
Toxicity (toxicology) Synthetic Coolants Laboratory animals CNS effects Spacecraft						

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