



National Toxicology Program
Toxicity Report Series
Number 56

**NTP Technical Report
on the Toxicity Studies of**

Carisoprodol

(CAS No. 78-44-4)

**Administered by Gavage
to F344/N Rats and B6C3F₁ Mice**

August 2000

**U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health**

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Toxicity Study Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals.

These studies are designed and conducted to characterize and evaluate the toxicologic potential of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Toxicity Study Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's toxic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). Other information about NTP studies is available at the NTP's World Wide Web site: <http://ntp-server.niehs.nih.gov>.

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**U.S. Department of Health and Human Services
Public Health Service
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PEER REVIEW

The draft report on the toxicity studies of carisoprodol was evaluated by the reviewers listed below. These reviewers serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, reviewers determine if the design and conditions of these NTP studies are appropriate and ensure that the Toxicity Study Report presents the experimental results and conclusions fully and clearly.

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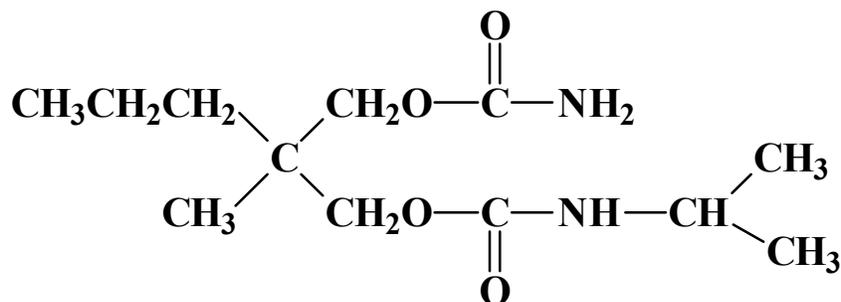
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ABSTRACT



CARISOPRODOL

CAS No. 78-44-4

Chemical Formula: $C_{12}H_{24}N_2O_4$ Molecular Weight: 260.33

Synonyms: Carisoprodol; isobamate; isopropyl meprobamate; N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate; (1-methylethyl)carbamic acid 2-[[[(aminocarbonyl)oxy]methyl]-2-methylpentyl ester

Trade names: Apesan; Arusal; Caprodat; Carisoma; Domarax; Flexal; Flexartal; Miolisodal; Mioril; Rela; Relasom; Sanoma; Soma; Somadril; Somalgit

Carisoprodol is a widely used skeletal muscle relaxant and analgesic and is available as a prescription drug. Comparative studies were conducted to determine the toxicity of carisoprodol administered in corn oil and in 0.5% methylcellulose by gavage. Carisoprodol plasma concentrations of rats and mice were measured at the end of the 13-week studies; single-dose plasma carisoprodol analyses were also performed. Genetic toxicity studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, cultured Chinese hamster ovary cells, and peripheral blood erythrocytes of mice.

Groups of 10 male and 10 female F344/N rats received 0, 100, 200, 400, 800, or 1,600 mg carisoprodol per kilogram body weight in corn oil by gavage or 0, 100, 200, 400, or 800 mg/kg carisoprodol in 0.5% methylcellulose by gavage for 13 weeks. Groups of 10 male and 10 female B6C3F₁ mice received 0, 75, 150, 300, 600, or 1,200 mg/kg carisoprodol in corn oil by gavage or 0, 600, 1,200, or 1,600 mg/kg carisoprodol in 0.5% methylcellulose by gavage for 13 weeks.

Among rats that received carisoprodol in corn oil, survival was similar to that of the vehicle controls. Survival of rats administered carisoprodol in 0.5% methylcellulose was also similar to that of the vehicle controls after adjustment for deaths (two males and one female in the 800 mg/kg group and two females in the 400 mg/kg group). The final mean body weight gain of males administered 1,600 mg/kg carisoprodol in corn oil was significantly less than that of the vehicle controls; the final mean body weights and body weight gains of female rats in the 800 and 1,600 mg/kg groups were significantly greater. In the carisoprodol in 0.5% methylcellulose study, males in the 200 mg/kg group and females in the 100 and 800 mg/kg groups had significantly greater mean body weights and body weight gains than did the vehicle controls. Clinical findings in rats administered carisoprodol in corn oil or in 0.5% methylcellulose included lethargy, ataxia, diarrhea, and prostration; the incidences were dose-related, and females were more sensitive than males to the effects of carisoprodol.

In the carisoprodol in corn oil study, differences in hematology and clinical chemistry parameters occurred with no consistent patterns. The effects of carisoprodol in 0.5% methylcellulose on hematology and clinical chemistry parameters were not studied.

In the corn oil study, the kidney and liver weights of male and female rats administered 200 mg/kg carisoprodol or greater were generally significantly greater than those of the vehicle controls. In the 0.5% methylcellulose study, liver weights were significantly greater in male rats administered 400 or 800 mg/kg and in female rats administered 800 mg/kg carisoprodol compared to the vehicle controls; however, a consistent effect on the kidney weights was not observed.

Nephropathy was observed in male rats administered 400 mg/kg carisoprodol or greater in corn oil; the livers of four males in the 1,600 mg/kg group had centrilobular hypertrophy of hepatocytes. No lesions were observed histopathologically in female rats administered carisoprodol in corn oil. In the carisoprodol in 0.5% methylcellulose study, the severity of nephropathy in males administered 200 mg/kg or greater was enhanced, and the incidence of nephropathy in female rats in the 800 mg/kg group was slightly greater than that in the vehicle controls.

Plasma carisoprodol concentrations at the end of 13 weeks generally increased with increasing dose in rats administered carisoprodol in corn oil or in 0.5% methylcellulose. The plasma carisoprodol concentrations in rats administered a single gavage dose of carisoprodol in corn oil also increased with increasing dose.

In the carisoprodol in corn oil mouse study, two females each in the vehicle control and 75 mg/kg groups and one female each in the 150 and 600 mg/kg groups were accidentally killed; all males survived to the end of the

study. One male and one female administered 1,600 mg/kg carisoprodol in 0.5% methylcellulose died; seven mice were accidentally killed. The mean body weights and body weight gains of mice administered carisoprodol in corn oil were generally similar to those of the vehicle controls. The final mean body weights and body weight gains of all groups of males and females administered carisoprodol in 0.5% methylcellulose were significantly less.

Clinical findings in the carisoprodol in corn oil study included lethargy, ataxia, tremors, and prostration in male and female mice. Ataxia, lethargy, convulsions, and prostration were observed in all dosed groups of males and females administered carisoprodol in 0.5% methylcellulose. In the carisoprodol in corn oil study, liver weights were significantly greater in males administered 300 mg/kg or greater and in females administered 150 mg/kg or greater than in the vehicle controls.

In the carisoprodol in corn oil study, no gross or microscopic lesions were considered related to carisoprodol administration. Minimal to mild centrilobular hypertrophy was observed in the liver of all dosed groups of males and in females in the 1,200 and 1,600 mg/kg groups in the carisoprodol in 0.5% methylcellulose study.

The testis weights of males administered 1,200 mg/kg carisoprodol in corn oil were significantly less than those of the vehicle controls; the sperm motility of males in this group was also significantly less than that of the vehicle controls. There were no significant differences in vaginal cytology parameters between dosed and vehicle control females.

At the end of the carisoprodol in corn oil study, the concentration of carisoprodol was above the limit of detection in the plasma of only one male mouse each in the 300 and 1,200 mg/kg groups and in four females in the 1,200 mg/kg group. In mice administered a single gavage dose of carisoprodol in corn oil, plasma concentrations increased with increasing dose; peak plasma concentrations occurred at 20 to 120 minutes in males and 60 to 120 minutes in females. In the carisoprodol in 0.5% methylcellulose study, plasma carisoprodol concentrations of female, but not male, mice increased with increasing dose; peak plasma carisoprodol concentrations occurred at 30 minutes postdosing in all groups of males and females.

Results of proportionality and bioavailability studies indicated that single gavage doses of 200 to 800 mg/kg carisoprodol in 0.5% methylcellulose in rats or 300 to 1,200 mg/kg in mice were dose proportional; absolute bioavailability values increased with increasing dose, ranging from 15% to 32% for rats and from 18% to 38% for mice. For rats, the bioavailability of carisoprodol in 0.5% methylcellulose was approximately fivefold that of carisoprodol in corn oil; the C_{\max} values of the dose in 0.5% methylcellulose were approximately threefold

those of the dose in corn oil. For mice, no significant difference was observed in the bioavailability of carisoprodol between the vehicles; however, the C_{\max} values of the dose in 0.5% methylcellulose were 1.5 to 1.75 times those of the dose in corn oil.

Carisoprodol was not mutagenic in any of four strains of *Salmonella typhimurium*, with or without S9 metabolic activation. It did induce mutations in L5178Y mouse lymphoma cells in the absence of S9; with S9, no mutagenic activity was noted in this assay. Results of the sister chromatid exchange test with carisoprodol in cultured Chinese hamster ovary cells were considered equivocal with and without S9. Chromosomal aberrations in cultured Chinese hamster ovary cells were clearly increased by carisoprodol treatment, particularly in the presence of S9. No significant increases in the frequency of micronucleated erythrocytes were observed in peripheral blood samples from male and female mice administered carisoprodol by gavage for 13 weeks.

In conclusion, carisoprodol induced ataxia and prostration in rats and mice, increases in liver weights in rats and mice, and nephropathy in male rats. The bioavailability of carisoprodol in 5% methylcellulose was greater than in corn oil. The no-observed-adverse-effect (NOAEL) level of carisoprodol administered in corn oil or in 0.5% methylcellulose was determined to be 100 mg/kg, compared to the clinical dose of 20 mg/kg per day for adults and 5 to 7.5 mg/kg per day for children.