Lubrizol

TECHNICAL DATA SHEET

**TDS-328**
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# Regulatory Information for Carbopol®* 971P NF Polymer & Carbopol® 71G NF Polymer
## (Toxicology Support Summary)

## GRAS Information

With regard to the GRAS status of Carbopol® 971P NF polymer, Carbopol® 71G NF polymer and Carbopol® 974P NF polymer, both products have been self-determined by Lubrizol Advanced Materials, Inc. to be GRAS when used in vitamin tablets which are considered food supplements or nutraceuticals. Lubrizol Advanced Materials, Inc. has gone to outside experts in both the legal and technical area to evaluate this determination and they have given us their written opinion on this claim. This is in complete accord with FDA accepted policy. The US FDA does not require that self-determined GRAS evaluations be confirmed. Based on that opinion we have made the following projections:

1) That use levels of our products could be up to 30% of the tablet mass, with a typical use of 15 - 20%, and

2) That the average weight of the vitamin tablet is 500 mg (based on information from the Physician's Desk Reference, 48th Edition, 1994).

Based on these assumptions the estimated daily intake of Carbopol® 971P NF polymer or Carbopol® 974P NF polymer present in vitamin tablets at the 20% level would be 1.7 mg/kg/day assuming a 60 kg individual. Based on this, it is our opinion that these products in this use range are properly considered GRAS for their intended use in food supplements. The FDA does have authority in the food supplement area to declare products not acceptable due to being adulterated or being unsafe. Lubrizol Advanced Materials, Inc. is not aware of any product that has been rejected by FDA due to the use of Carbopol® polymers.

Lubrizol Advanced Materials, Inc. has not applied for and believes it not necessary to apply for Carbopol® polymer products to be considered as GRAS for similar applications to vitamin tablets. Customers must evaluate their total dose formulation that might include Carbopol® polymers and be confident that they are producing an acceptable finished dosage based on their knowledge of how the entire dose is presented. The FDA does not have an approved daily intake amount of Carbopol® 971P polymer or Carbopol® 974P polymer. Products using higher than typical amounts could be evaluated on a case by case basis, but there is no reason that we are aware of that would cause concern or rejection. Lubrizol Advanced Materials, Inc. has likewise not established a safe daily intake for this chemical.

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However, Lubrizol Advanced Materials, Inc. has conducted repeat dose feeding studies in rats and dogs with Carbopol® 974P NF polymer and has determined that these studies are applicable to and predictive of he toxicity of Carbopol® 971P NF polymer. Furthermore, Lubrizol Advanced Materials, Inc. has made this information available to the FDA for their evaluation of new drugs as part of our Drug Master File on these products. Lubrizol Advanced Materials, Inc. will also make this information available to FDA's Office of Generic Drugs upon customer request to support that customer's generic or OTC drug application.

## Toxicology Information

In a 90 day study of Carbopol® 974P NF polymer with dogs, the no observed adverse effect level (NOAEL) was 50,000 ppm (1,656.6 mg/kg/day for males; 1,641.8 mg/kg/day for females)[1]. In a 90 day study of Carbopol® 974P NF polymer with rats, the no observed adverse effect level (NOAEL) was 25,000 ppm (1,512.6 mg/kg/day for males; 1,680.7 mg/kg/day for females)[1]. The effects at 50,000 ppm (3,147.1 mg/kg/day for males; 3,415.8 mg/kg/day for females) were limited to decreases in body weight and mild changes in some clinical parameters which were deemed to be consistent with a nutritional deficit.

The details of the changes in body weight (the means and standard deviations) are as follows:

- No significant differences were observed in females at any time point or at any concentration compared to the controls. In males, body weight means were decreased week 4 (374 g ± 20.2 g at 50,000 ppm vs. 409 g ± 34.0 g in the control, 0 ppm), at week 9 (440g ± 38.7 g at 50,000 ppm vs. 486g ± 45.3 g in the control, 0 ppm), and at week 14 (472 g ± 39.6 g at 50,000 ppm vs. 529 g ± 52.2 g in the control, 0 ppm).

- Comparison of body weight changes, means and standard deviations: Mean body weight changes were not significantly different at any time or at any level compared to the controls. However comparisons of aggregate body weight changes over the 13 week exposure period indicated that body weight gain was significantly reduced at the 50,000 ppm level in both males and females. In males, body weight gain was 240 g ± 34.7 g at 50,000 ppm vs. 293 g ± 44.1 g in the control, 0 ppm). In females, body weight gain was 106 g ± 19.0 g at 50,000 ppm vs. 139 g ±19.0 g in the control, 0 ppm).

- We do not have any reason to believe that Carbopol® 974P NF polymer/Carbopol 971P NF polymer would hinder the absorption of nutrients. The effects noted in rats are believed to be due to the fact that Carbopol® polymers do not have any nutritional value. The effect noted at 50,000 ppm (5% in the diet) is consistent with a deficit in the total caloric intake necessary for normal weight gain. No pattern of toxicologically significant systemic effects was evident in rats. No effects were noted at 25,000 ppm in rats. No effects were noted at 50,000 ppm in dogs. The NOAEL's for dogs and rats are very similar when compared on a mg/kg/day basis. These studies did not include recovery groups.

The entire study can be shared with customers under appropriate confidentiality documents.

[1] The reason that the dog and rat consume approximately the same amount of compound intake on a mg/kg/day basis (see NOAELS above) at 50,000 ppm and 25,000 ppm, respectively, is that the rat consumes approximately twice as much food on an a mg/kg/day basis than the dog. This is consistent with the rat's higher metabolic rate.

## Residuals and Absorption

The residual solvent (ethyl acetate), as well as all the other ingredients used to produce Carbopol® 971P NF polymer, are *identical* to those used to produce Carbopol® 974P NF polymer. Carbopol® 974P NF polymer is currently used in several FDA approved drug formulations. Again, Lubrizol Advanced Materials, Inc. has conducted repeat dose feeding studies in rats and dogs with Carbopol® 974P NF polymer and has determined that these studies are applicable to and predictive of the toxicity of Carbopol® 971P NF polymer. As for Carbopol® 971P NF polymer, we do not expect that the residual solvent (ethyl acetate, a class III solvent according to ICH guidelines), will raise any new issue, but we cannot provide any predictions on the probability of success in obtaining drug approval for any specific application.

Lubrizol Advanced Materials, Inc. believes that absorption from the gastrointestinal tract of Carbopol® 971P NF polymer does not occur based on the fact that this molecule is extremely large and will not pass through the walls of the intestine (see Genotoxicity Evaluation below). The molecular weight of both Carbopol® 971P NF polymer and Carbopol® 974P NF polymer is in the range of billions of Daltons. This is consistent with work done outside Lubrizol Advanced Materials, Inc. by others using $C^{14}$ labeled cross linked and uncross linked polyacrylic acids [See Riley et al. (2001) "The Gastrointestinal Transit Profile of $C^{14}$ Labeled Poly (Acrylic Acids): an In Vivo Study." Biomaterials, 22:1861-1867]. No evidence of systemic absorption was identified, even for lower molecular weight, uncrosslinked fractions of the polyacrylic acid. This is consistent with our polymer knowledge regarding the statistical nature of the products we produce. If the monomer, which is measured and reported on our certificate of analysis, is within specification, then the toxicology of our finished product will meet the use criteria for oral applications. The toxicology of pure acrylic acid is well known, and other oligomers that are there at lower levels than the monomer, should have the same or better toxicology profile.

## Genotoxicity Evaluations

Generally, we do not conduct genotoxicity evaluations of high molecular weight polymers. In the 1984 final polymer exemption rule (49 FR No. 226, Nov. 21, 1984) EPA established 1000 Dalton as the threshold for exempting polymers. The agency noted that molecular weight is a determinant of risk and stated that,

"For a chemical to elicit a toxic response within an organism, it must come into direct contact with the biological cells from which it elicits the response. "

The Agency went on to state that,

"If a chemical cannot penetrate the protective membranes to access a target site, it usually cannot elicit a response in the organism no matter what inherent potential it may have to do so. It can be further reasoned that if a chemical cannot elicit a response, it will not present a risk."

The Agency concluded that,

"---substances with molecular weights greater than 400 are not readily absorbed through the intact skin and that substances with molecular weights greater than 1000 are not readily absorbed through the gastrointestinal tract."

## Other Testing

Information on the chemistry and hazards of the ingredients that are used in our products and of the impurities (i.e., residual monomers, additives) is used to assess the genotoxic hazards and potential risks of our final product. This information, along with other data, also is used to prepare our MSDS's and labels in accordance with the applicable regulations.

Lubrizol Advanced Materials, Inc. has not conducted any photo safety studies with Carbopol® 971P NF polymer. However, photo testing of Carbomer 934 (Carbopol® 934 polymer) is described in "The Final Report on the Safety Assessment of Carbomers-934, -910, -934P, -940, and -962", J. Amer. College Toxicol. 1(2):109-141.