This bulletin discusses toxicological investigations of AQUALON® cellulose gum (purified sodium carboxymethylcellulose). These data will be of special interest to the cosmetic and pharmaceutical industries.

Subacute and chronic oral toxicity studies in rats, guinea pigs, dogs, and humans demonstrate that cellulose gum, or purified sodium carboxymethylcellulose, possesses no systemic toxic properties. Very high levels, such as 10% of the diet, possess a laxative effect consistent with the hydrophilic properties of the product and similar to sodium alginate and karaya gums. Gastrointestinal absorption studies in rats demonstrate that cellulose gum is not absorbed from the intestinal tract. All these studies lead to the conclusion that, on ingestion, cellulose gum is physiologically inert.

Chemical Composition
Aqualon cellulose gum is the sodium salt of carboxymethylcellulose especially purified to a minimum assay of 99.5% by removal of reaction salts and other impurities. It is available in a variety of viscosity ranges and degrees of substitution. The USP grade of cellulose gum destined for pharmaceutical and cosmetic applications is rigorously controlled as to chemical purity. The purification limitation of 99.5% is considered most important for these grades, since the reduction in salt content by a factor of more than 80 guarantees that the product has been washed free of undesirable low molecular weight polymers.

Physical Properties
Aqualon cellulose gum is a light cream to white granular material that is inert to change in color and taste. It is soluble in hot or cold water and has good tolerance for ethanol and acetone. It is generally unaffected by other organic materials such as oils, greases, and solvents. Cellulose gum is compatible with a wide range of natural and synthetic water-soluble gums and salts.
Manufacturing and Handling

Quality assurance begins with careful selection and analysis of raw materials. Accurate records are kept to meet FDA and USP standards. Manufacturing process conditions are tightly controlled, and monitoring data on each operating parameter are recorded and filed. Special attention is paid to cleaning and inspection of equipment. As required by regulatory agencies, USP grades of cellulose gum are stored separately from other grades; temperature and humidity are controlled; and possibility of contamination by other materials is eliminated. A great number of qualitative and quantitative analytical tests are performed on pharmaceutical and cosmetic grades to ensure meeting all purity criteria. Records of these tests are regularly maintained, since the plant and its records are subject to inspection by teams representing the FDA to check for compliance with drug raw material manufacturing standards.

Skin Irritation and Sensitization

Two hundred human volunteers have been patch-tested by the Schwartz technique with no evidence of primary skin irritation or sensitization from cellulose gum.

Eye Irritation

Application to the eyes of New Zealand albino rabbits of 10 mg of powdered cellulose gum produced slight irritation, which cleared completely in about 72 hrs without washing out the eyes.

Application to the eyes of 0.1 mg of cellulose gum, in the form of a 0.1% aqueous suspension, produced very slight irritation, which cleared completely in about 24 hrs without washing out the eyes.

Acute Oral Toxicity

Oral administration of suspensions of cellulose gum in olive oils were given to white rats and guinea pigs. The following results were noted:

<table>
<thead>
<tr>
<th></th>
<th>Acute Oral LD_{50}</th>
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<tbody>
<tr>
<td>Rats</td>
<td>27 g/kg body weight</td>
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<tr>
<td>Guinea pigs</td>
<td>16 g/kg body weight</td>
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Six-Month Oral Toxicity

One hundred rats, 100 guinea pigs, and 10 dogs were fed dietary levels of 1 and 2% (0.5 and 1.0 g of cellulose gum per kg of body weight added to the diet daily) for 6 months. Normal growth, fertility, urinalysis, and hematology were observed during the course of the experiment, and no gross or microscopic pathology was detected at termination.

Three dogs were also fed dietary levels of 5 and 10% for 6 months. Pure grades of sodium alginate and karaya gum were fed for comparison at a level of 10%. At the 5% level, all observations during the experiment and at termination were normal. At the 10% level, growth was retarded with cellulose gum, as well as with sodium alginate and karaya gum. Loose stools were observed with all three products. No other changes (urinalysis, hematology, gross and microscopic pathology) were detected. Attempts to feed 20% cellulose gum in the diets of dogs were unsuccessful, owing to food refusal.

One-Year Oral Studies

Twenty guinea pigs were fed dietary levels of 1 and 2% (0.5 and 1.0 g/kg daily added to the diet) for 1 year. No mortality occurred; growth was normal; and, at termination, no gross or microscopic pathology was detected.
Chronic Oral Toxicity

Twenty-five rats were fed dietary levels of 0.2, 1, and 2% (0.1, 0.5, and 1.0 g/kg added to their diet) for 2 years. Mortality, growth, monthly urinalysis, and hematology were normal. Gross and microscopic examination after 25 months’ feeding revealed no pathology other than the senility changes present in controls. No neoplasms were found in any of the rats fed cellulose gum.

Reproduction

Rats fed dietary levels of 0.2, 1, and 2% cellulose gum were carried through three-generation reproduction studies, with offspring being maintained on these same dietary levels. No alterations in fertility or reproduction of these animals were detected.

Gastrointestinal Absorption

Radioactive purified cellulose gum, manufactured with C\textsuperscript{14}-tagged sodium chloroacetate, was administered to rats as an aqueous solution at a dosage of 1.3 g/kg. Urine was collected in special metabolism cages to prevent cross-contamination with feces. Forty-four hours after dosing, the livers and kidneys were analyzed for radioactivity. None was found at a sensitivity equivalent to less than 0.02% of the administered dose. Urine specimens showed an average activity equivalent to 0.14% of the administered dose. This activity corresponded to the amount of radioactive salt (sodium glycolate) formed in the synthesis, and was established by chromatography of the urine solid not to be NaCMC or other saccharide polymer.

Clinical Studies

Eleven human volunteers ingested 10 g of cellulose gum each day for 6 months. Complete hematology and urinalysis on all subjects revealed no alterations during administration. Bone marrow studies were made on three subjects during the test and six subjects at completion; all were within normal limits. Some additional volunteers experienced a laxative effect at 10 g daily. No other physiological manifestations were detected.

Toxicity to Fish

Employing a standard laboratory procedure, rainbow trout and bluegills were exposed under static conditions to technical-grade CMC at several concentrations, up to a maximum level of 100 ppm, and observed for mortality or other adverse reaction over a period of 96 hrs. Results of this 96-hr observation demonstrate that CMC has a 4-day median tolerance limit (TL\textsubscript{50}) of greater than 100 ppm, the highest level tested. In addition, no adverse reactions were noted in the fish exposed to CMC. These results demonstrate that CMC has a low order of toxicity to fish.