NITROCELLULOSE

Health Advisory

Office of Drinking Water
U.S. Environmental Protection Agency
Washington, DC 20460

PREFACE

This report was prepared in accordance with the Memorandum of Understanding between the Department of the Army, Deputy for Environment, Safety and Occupational Health (OASA(I&L)) and the U.S. Environmental Protection Agency (EPA), Office of Drinking Water (ODW), Criteria and Standards Division, for the purpose of developing drinking water Health Advisories (HAs) for selected environmental contaminants, as requested by the Army.

Health Advisories provide specific advice on the levels of contaminants in drinking water at which adverse health effects would not be anticipated and which include a margin of safety so as to protect the most sensitive member of the population at risk. A Health Advisory provides health effects guidelines and analytical methods and recommends treatment techniques on a case-by-case basis. These advisories are normally prepared for One-day, 10-day, Longer-term and Lifetime exposure periods where available toxicological data permit. These advisories do not condone the presence of contaminants in drinking water; nor are they legally enforceable standards. They are not issued as official regulations, and they may or may not lead to the issuance of national standards or Maximum Contaminant Levels (MCLs).

This report is the product of the foregoing process. Available toxicological data, as provided by the Army, on the munitions chemical, nitrocellulose (NC), have been reviewed, and the relevant findings are presented in this report in a manner so as to allow for an evaluation of the data without continued reference to the primary documents.

Significant chemical and physical properties of NC as well as potential sources of exposure are provided as a means of identifying the subject chemical. Data on the pharmacokinetic properties, although somewhat limited in scope, are summarized. All available toxicological data, including short-term, longer-term and lifetime feeding studies in three species, as well as the results of reproductive and genetic toxicology studies, have been reviewed, and those effects deemed relevant to the ingestion of NC are summarized. Results of immunologic and carcinogenic studies are also included.

This report also includes a section describing state-of-the-art methods of analyses for NC in drinking water and includes essential treatment techniques appropriate for NC removal from an affected water supply, should the levels of NC in the drinking water reach a level considered unpalatable due to taste, clarity or similar indicators.

This report has been submitted to a critical review by the EPA to include a panel of Health Effects Branch (HEB) toxicologists. Their comments, as appropriate, have been incorporated into this report.

A companion document, "Data Deficiencies/Problem Areas and Recommendations

for Additional Data Base Development for Nitrocellulose" is included in this report under Appendix 2.

I would like to express my thanks to Dr. John Glennon, Life Systems, Inc., who afforded valuable coordination and logistical assistance. I also thank Dr. Janet Normandy, Ms. Lori Gordon and Dr. William Hartley who provided the extensive technical skills required for the preparation of this report.

I am grateful to the following members of the EPA Tox-Review Panel, Dr. Kenneth Bailey, Dr. Ambika Bathija, Dr. Bill Marcus and Mr. Bruce Mintz, who took time to review this report and to provide their invaluable input.

Finally, I would like to thank Dr. Edward Ohanian, Chief, Health Effects Branch, Dr. Joseph Cotruvo, Director Criteria and Standards Division, and Dr. Penelope Fenner-Crisp, Manager, Health Advisory Program, for providing me with the opportunity and encouragement to be a part of this project.

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I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The Advisories are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit and Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based upon differing assumptions, the estimates that are derived can differ by several orders of magnitude.

II. GENERAL INFORMATION

As described by Sullivan et al. (1978), nitrocellulose, or cellulose trinitrate, is a non-volatile, fibrous, cotton-like, white solid (specific gravity 1.66) consisting of chains of beta, 1 to 4 linked glucoside units in which the hydroxyl groups of the glucose subunits have reacted to form nitrate esters. The chemical formula is approximately $[C_6H_7O_2(ONO_2)_3]_n$; the molecular weight depends on chain length, and the degree of polymerization (DP) varies appreciably. Cotton linters and wood pulp used for the preparation of military grades of NC have a DP of approximately 1,000 to 1,500. The fully nitrated form of NC has a nitrogen content of 14.14% and a formula weight of 297.14. This degree of nitration is difficult to accomplish (Department of the Army Technical Manual TM9-1300-214, 1967). Nitrocellulose is extremely flammable and has a flash point of 12.8°C. The melting point range is 160° to 170°C -- also its autoignition temperature.

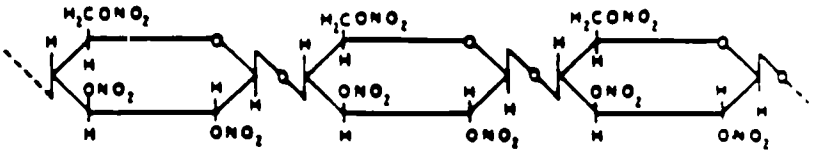
"Guncotton", military grade cellulose nitrate, contains 13.5% nitrogen and is the most highly nitrated form. Theoretically, mononitrated, dinitrated, and trinitrated cellulose contain 6.8% N, 11.1% N, and 14.1% N, respectively. "Guncotton" is essentially fully nitrated and, therefore, can be considered to be a crude cellulose trinitrate contaminated by traces of less completely nitrated esters (Sullivan et al., 1978). The general properties of cellulose trinitrate are summarized in Table II-1.

The nitrate esters, in general, are soluble in esters, aldehydes, and ketones. The more completely nitrated a cellulose is, however, the smaller the range of materials in which it is soluble. The less nitrated forms of cellulose nitrate are also very soluble in methanol, benzene, toluene, and mixtures of ether and ethanol. These compounds (pyroxylin: 8% to 12% N and pyrocellulose: 12.5% N) are forms of collodion and are used chiefly as lacquers, ink bases, and filter membranes, and in veterinary medicine for wound closure. Cellulose trinitrate is insoluble in water, ethanol, ethyl ether, and benzene but completely miscible in acetone, methylethyl ketone, tetrahydrofuran, as well as nitrobenzene and ethyl-, butyl-, and amylacetates (Sullivan et al., 1978).

Nitrocellulose is resistant to biological degradation and is a persistent compound in the environment. It has been suggested by Sullivan et al. (1978) that cellulose triacetate and cellulose trinitrate are resistant to enzymatic attack. These authors further stated that although direct biodegradation of nitrocellulose does not seem to be feasible, alkaline hydrolysis yields material that can be decomposed by microbial activity. Nitrocellulose, therefore, can be characterized as being persistent in the environment unless chemically altered.

Based on an extensive volume of literature dealing with the adsorptive capacity of nitrocellulose for biologically important macromolecules, Sullivan et al. (1978) have indicated that nitrocellulose strongly adsorbs and concentrates DNA and various RNA molecules from solution, and adsorbs proteins and polypeptides under various conditions. Proteins with an uncoiled structure or molecular weight greater than 10^5 are strongly bound. Denatured proteins are also strongly adsorbed, especially under acidic conditions.

TABLE II-1 GENERAL CHEMICAL AND PHYSICAL PROPERTIES OF CELLULOSE TRINITRATE[a/]

CAS Number	9004-70-0
Names	Cellulose trinitrate; nitrocellulose; guncotton
Molecular weight	Varies with chain length
Empirical formula	$[C_6H_7O_2(ONO_2)_3]_n$
Structure	
Color	Whitish
Physical state	Fibrous solid
Specific gravity	1.66
Percent nitrogen	14.1[b/]
carbon	24.3
oxygen	59.3
hydrogen	2.4
Solubility characteristics	Insoluable in water, ethanol, benzene and most other solvents. Soluble in 25 parts of 1:3 alcohol:ether; soluble in acetone in all proporations; soluble in methylethyl ketone, nitrobenzene, tetrahydrofuran, and ethyl, butyl and amylacetate.
Melting point	160-170° C
Autoignition temperature	160-170° C
Flash point	12.7° C

a/ References: Sullivan et al., 1978; Hawley, 1981; RTECS, 1986.
b/ Approximate, depends on processing and chain length.

III. SOURCES OF EXPOSURE

Nitrocellulose (NC) is a principal ingredient of propellants, smokeless powder, rocket fuel, ball powder, mortar increments, and some explosives (Rosenblatt et al., 1973). It is produced for military use at selected Army ammunition plants (AAP) by treating cotton linters or wood pulp with mixed nitric and sulfuric acids at 30°C. The resulting slurry is centrifuged to remove most of the acid, treated with several changes of boiling water, washed with a heavy stream of water, and finally screened to remove most of the water (Department of the Army Technical Manual TM9-1300-214, 1967). Production requires 16 to 22 gallons of process water per pound of NC produced. Most of this water is discharged and contains, in addition to NC, 0.7 to 1.0 pound of sulfuric acid and 0.3 to 0.4 pound of nitric acid per pound of NC produced, thus resulting in a low pH (Rosenblatt et al., 1973; Helton, 1976). Nitrocellulose fines are found in production wastewater because of settling pit overflow and some escape after flowing through the waste acid neutralization process lines (Huff et al., 1975). Helton (1976) analyzed samples of NC fines from wastewaters of an AAP and found that more than 99% of the particulate material was military grade NC with an average nitrogen content of 12.9% and particle size greater than 5 microns. Sullivan et al. (1978) indicated that these data suggested that suspended solids below 0.8 microns contained significant portions of nonnitrated cellulose and other materials while those greater than 44 microns were mostly NC.

IV. PHARMACOKINETICS

There are currently no available data to suggest that nitrocellulose can be absorbed from any route. A study in rats has shown that NC appears to remain within the gastrointestinal tract until it is excreted in the feces. Other available data are inconclusive.

Ellis et al. (1976) studied the absorption, distribution, and excretion of ^{14}C-nitrocellulose (prepared from cotton grown in the presence of D-glucose-UL-^{14}C and nitrated by standard procedures) in two male Charles River CD rats. Each rat was fasted overnight before being given NC orally either in an aqueous suspension or in a suspension of 0.2% methyl cellulose-0.4% Tween 80 (MC-TW80) at a volume of 1 ml/100 gm (presumably bodyweight; about 20,000 dpm/ml). After dosing, each rat was placed immediately in a "Roth-Delmar" metabolism chamber. Expired CO_2, feces, and urine were each collected separately in the apparatus. To ensure that sufficient radioactivity was administered, the dosing was repeated daily for 4 days. Twenty-four hours after the last dose, the animals were anesthetized and aortic blood was collected. Liver, spleen, brain, kidneys, lungs and thigh muscle along with the stomach, small intestine, cecum, large intestine and their contents were removed and each assayed for radioactivity via liquid scintillation spectrometry.

After repeated oral doses of radiolabeled nitrocellulose, no detectable radioactivity was found in any tissue or body fluid. Radioactivity was recovered only in the various components of the gastrointestinal (GI) tract plus contents and in the feces (percentage dpm recovered not specified). From these results, the authors concluded that the nitrocellulose molecule was not absorbed by the rat.

Ellis et al. (1980) conducted a mass-balance metabolism study of nitrocellulose using a dog fed 90 g (mg/kg dose could not be determined from data provided) of wet nitrocellulose (27.9 g dry weight). After 24, 48, 72 and 96 hours, the feces were collected and analyzed by the method of Selig (1961) which involves reduction of nitro groups and titration to a colorimetric endpoint. During the first 48-hour period, 9.5 g (dry weight) of NC were recovered representing a recovery of 34% (g recovered/g fed, dry weight). No further nitrocellulose was identified in later fecal samples. We can draw no useful generalizations from these results since they could indicate either that the method of analysis was not particularly effective, that some nitrocellulose may have been absorbed from the digestive tract of this dog, or that NC was denitrated by gut bacteria.

V. HEALTH EFFECTS

Currently available studies on the health effects of nitrocellulose suggest that it is not "toxic" unless ingested in enormous quantities such as 10% of the total diet. In those cases, death from intestinal impaction may occur just as it does in animals fed the same dietary levels of non-nitrated cotton linters.

A. Short-Term Exposure

The acute oral toxicity of nitrocellulose is very low in mice and rats as evidenced by LD_{50}'s of more than 5,000 mg/kg in both species. No acute toxicity data of nitrocellulose are provided in the 1986 edition of the Registry of Toxic Substances (RTECS, 1986).

Lee et al. (1975) used male and female Charles River rats and male and female albino Swiss mice (apparently 10/sex/dose; number and range of doses not clearly specified) to determine the acute oral LD_{50} of nitrocellulose. Each dose of nitrocellulose, suspended in water at a final concentration of 5% NC (dry weight basis), was divided in half and given 30 minutes apart due to the large volume necessary to administer a dose of 5,000 mg/kg (the authors did not indicate the volume administered). Test animals were fasted for at least 16 hours prior to oral dosing via gastric intubation. After treatment, the survivors were observed daily for 14 days for delayed mortality or signs of toxicity. The LD_{50} was calculated by a computer program based on the method of maximum likelihood of Finney (1971). The LD_{50}'s for nitrocellulose in male and female rats and in male and female mice were greater than 5,000 mg/kg. No toxic signs were observed in animals receiving the highest dose of nitrocellulose. Two of 10 male mice given 5,000 mg/kg died without any apparent gross lesions. No other animals died at any dose level.

1. Primary Skin and Eye Irritation

Using the modified Draize method for skin and eye irritation, a 33% concentration of NC in water was applied directly to the eye or shaved skin of the rabbit and evaluated at 24 and 72 hours (Lee et al., 1975). This concentration of NC was not irritating to either rabbit skin or eye.

B. Longer-Term Exposure

1. Thirteen-Week Studies

No adverse effects that can be related to the chemical characteristics of nitrocellulose were identified in the available thirteen-week studies in dogs, rats, and mice (Ellis et al., 1976). Intestinal blockage was the cause of death in high-dose mice (10% NC) as well as in control mice fed the same amount of cotton linters (10% of total diet).

Ellis et al. (1976) conducted thirteen-week studies of the oral toxicity of nitrocellulose using dogs, rats and mice. In the studies with dogs, 20 young healthy beagle dogs (7.2 to 13.6 kg) were divided into five groups of two males and two females. Three groups were administered NC as 1%, 3%, or 10% of their feed as dry weight. (Table A1-1, Appendix A1, describes method used to calculate doses. Using the authors' data for body weight at week 4 and average intake data for weeks 1 through 4, these doses were calculated to correspond to approximately 518, 1,900 and 6,890 mg/kg/day, respectively, for males and 610, 2,976 and 8,485 mg/kg/day, respectively, for females.) The fourth group received a mixture of 10% (approximately 6,181 and 8,627 mg/kg/day, males and females, respectively, calculated as above) of cotton cellulose linters and served as a cotton control to determine if any observed effects were due to the passage of non-nutritive bulk through the gastrointestinal tract. The fifth group served as an untreated control.

The tests included hematology, clinical blood chemistry and bromosulfophthalein (BSP) retention tests. At termination, the dogs were sacrificed and examined for treatment-related gross lesions and organs were weighed. Various tissues were processed for microscopic examination of lesions.

Feeding NC to dogs at up to 10% of their diets or cotton linters at 10% for 13 weeks did not cause any adverse effects. Dogs fed 10% NC or linters ate about 15% more than the others, indicating the test materials were merely non-nutritive bulk. All dogs, including the untreated and cotton controls, showed some variations in body weight, peripheral blood elements and various clinical chemistry tests but all data were reported to be within normal limits. Nitrocellulose was not reported to cause any treatment-related gross or microscopic lesions.

In thirteen-week studies with rats, Ellis et al. (1976) used 40 male and 40 female young healthy CD rats divided into five groups, each consisting of eight males and eight females. Three groups of rats were fed NC at 1%, 3%, or 10% in the feed as dry weight. The fourth group, the cotton controls, was fed cotton linters as 10% of the feed. (Ref. Table A1-1: Using the authors' data for the body weights averaged from weeks 0, 4, 8 and 13 and the average intake over weeks 1 through 13, these doses correspond to approximately 667 and 2,366 mg/kg/day for 1% and 3%, respectively, in the males and 820 and 2,673 mg/kg/day, respectively, in the females. Measured intakes for the rats fed 10% NC or 10% cotton linters in the diet were more than double those of the untreated control rats. The authors indicated that at 10% NC or 10% cotton linters in the diet, enormous mounds of white fluffy material were scattered all around the cage. Therefore, actual intake of NC or cotton linters at 10% in the diet cannot be calculated with any degree of accuracy.) The fifth group, the untreated controls, was given the powdered standard rodent chow without NC. Experimental procedures were similar to those used with dogs (Ellis et al., 1976) except that BSP retention tests were not performed.

Nitrocellulose and the cotton linters at 10% in the feed apparently acted as a non-nutritive bulk ingredient which the rats attempted to remove. These rats gained less weight than did the untreated control rats. The authors concluded that this was because they did not absorb enough of the nutritive portion of the feed. Rats fed the low or middle levels of NC apparently received enough nutritional intake and gained weight comparably to the untreated controls. Nitrocellulose administration did not result in any significant changes in peripheral blood elements or clinical blood chemistry or any apparent gross or microscopic lesions. Observed changes in the absolute organ weights of the liver, kidney and spleen of male rats fed 10% NC or cotton linters were statistically significant when compared to untreated controls. These changes were attributed by the authors to depressed body weight gain, as evidenced by comparable organ weight/body weight ratios.

In the thirteen-week studies with mice, Ellis et al. (1976) used 40 male and 40 female young healthy albino Swiss mice divided into five groups, each consisting of eight males and eight females. The treated groups were fed the same diets as prepared for the rats: 1%, 3%, or 10% of NC as dry weight in feed. Control mice received either the powdered standard rodent chow alone (as untreated controls), or 10% of cotton linters (as cotton controls). (Ref. Table A1-1: Using the authors' data for the body weights averaged from weeks 0, 4, 8 and 13, and the average intake for weeks 1 through 13, these doses correspond to approximately 1,690 and 5,062 mg/kg/day for 1% and 3%, respectively, in males and 1,741 and 7,000 mg/kg/day, respectively, in females. As in the rat study previously described, the actual intake of 10% NC or 10% cotton linters in the diet cannot be calculated with any degree of accuracy due to excessive scattering of the fibers.) The procedures used were similar to those described for rats except that clinical blood chemistry tests were not performed in mice. Blood samples for terminal hematology were collected by heart puncture under ether anesthesia.

Mice fed the low, middle or high levels of NC showed no apparent adverse effects from the chemical nature of this compound. In the first few weeks of the study, there were weight losses and deaths, apparently due to the fibrous nature of the substance, in mice fed the high level (10%) of NC as well as in mice fed 10% of cotton linters. The authors concluded that deaths were due to the blocking of the lower part of the gastrointestinal tract by masses of the fibers, particularly in the regions where water is removed from the chyme. Additional animals from a chronic study (same shipment and identical levels of NC) were added to this 13-week study to compensate for the early losses. No adverse effects or changes were observed in peripheral blood elements nor were any treatment-related gross or microscopic lesions reported by the authors.

2. Lifetime Exposure

Long-term studies conducted in dogs, rats and mice indicated a dose-related increase in total feed consumption and decreases in weight gain in high-dose

NC-treated rats and mice. Histopathologic evaluations of dogs, rats and mice treated for up to 24 months showed naturally occurring (as opposed to treatment-related) lesions in the thyroid and lungs in dogs, the lungs in rats and several organs in mice (kidneys, adrenals, liver and intestines). Adverse effects causing early deaths due to intestinal impaction occurred in high-dose mice.

Ellis et al. (1980) studied the effects of NC administered orally at dose levels up to 10% NC in feed for dogs, rats and mice for 12 and 24 months.

Three groups of beagle dogs, six of each sex per group, were administered NC at 1%, 3% or 10% in the feed calculated on a dry weight basis for up to 24 months. (Ref. Table A1-1: Using the authors' data for the average body weight of 2 dogs/sex at 24 months and the average consumption [mean of 22 monthly measurements], these doses correspond to approximately 311, 1,013 and 4,070 mg/kg/day, respectively, for males and 344, 1,034 and 4,576 mg/kg/day, respectively, for females). Two additional control groups were run concurrently for each sex and were either untreated or received 10% cotton linters (cellulose linters; approximately 2,888 and 3,874 mg/kg/day, males and females, respectively, when calculated as above) in their diets. No toxic signs related to NC intake were seen in any of the dogs at any time.

Following 12 months of treatment without a recovery period, one male and one female per treatment group were sacrificed. Histopathological examination revealed a variety of "minimal to mild lesions" in all the dogs examined and moderate thyroid hyperplasia in a control and a high dose female and moderate thymus involution in a cotton control male. These lesions included microcalculi in the medula of the kidney, parafollicular cell hyperplasia of the thyroid, hemosiderosis of the spleen and axillary lymph nodes and involution of the thymus. The lesions were considered by the authors to be typical of those naturally occurring in dogs of the age tested and were, therefore, not considered treatment-related. Since there were no effects related to NC treatment, histologic data from the low and middle dose dogs were not evaluated, and the necropsy on the dogs in the recovery group (one/sex/treatment group) was omitted. No dose-related variations were reported for routine hematologic parameters nor in fasting blood glucose, serum transaminases (SGOT, SGPT), cholesterol, alkaline phosphatase and blood urea nitrogen (BUN). The body weights, absolute and relative organ weights were comparable to unexposed controls or cotton controls (10% linters). However, there was a dose-related increase in feed consumption.

Similarly, dogs (2/sex/treatment group) administered NC (up to 10%) for 24 months (without a recovery period) showed what the authors considered naturally occurring histopathologic lesions. These lesions included pituitary cysts, mild to severe chronic lymphocytic thyroiditis, pleural fibrosis, muscular hypertrophy of bronchioles, mild to moderate granulomatous pneumonia, renal calcinosis, extramedullary hematopoiesis of the spleen and hemosiderosis of the lymph nodes. The absolute and relative organ weights had some variations between individual dogs, but no apparent differences between dogs in different treatment groups.

Because there were no observable effects from feeding NC for 24 months, the necropsy on the dogs in the recovery group (2/sex/treatment group) was omitted.

Male and female rats (32/sex/treatment group) were similarly exposed to NC at 1%, 3%, or 10% in the feed on a dry weight basis for up to 24 months (Ellis et al., 1980). Controls, similar to those used in dog studies, were run concurrently. A separate group of rats, 8/sex/group, dosed as above, was started 6 months later and used for the one year necropsy and a 4-week recovery study. (Ref. Table A1-1: Using the authors' data for average terminal body weight at 24 months and the average consumption over 24 months [mean of 23 monthly measurements], these doses correspond to approximately 350 and 1,280 mg/kg/day for 1% and 3%, respectively, in males and to 373 and 1,422 mg/kg/day, respectively, in females.) Apparent feed intake for rats given 10% NC or 10% cotton linters was approximately twice by weight that of untreated controls. However, the authors indicated that these two groups had visible scattering of feed and fiber around the cages. This scattering would account for part of the loss of weight in the feeders (the parameter measured) and, therefore, the apparent increased intake (actual intake of NC or cotton linters at 10% in the diet) cannot be calculated with any degree of accuracy.

Following 12 months of treatment, all exposed rats showed a dose-related increase in food consumption. High dose and cotton control (10% linters) male rats failed to gain weight or lost weight in the first week and, thereafter, gained weight more slowly than the controls. The authors felt that this effect was consistent with the fact that NC serves as non-nutritive dietary bulk. Other than normal species variations, no significant effects were apparent for routine hematologic parameters nor for fasting blood glucose, SGOT, SGPT, cholesterol, alkaline phosphatase and BUN. Absolute and relative organ weights were generally comparable to controls with a few statistically significant differences (decrease in testes at 3% and spleen at 3% and 10%, linters and controls in males). The authors reported these effects as normal variations. Upon histologic examination, mild to moderate chronic murine pneumonia was found in all untreated control rats, cotton control rats, and the NC-treated rats at the high dose levels. A variety of other lesions was found in these rats including bile duct hyperplasia and mild to severe nephritis in males only and cystic degeneration of the adrenal gland, and excessive hemosiderin in the spleen of the females only. Tracheitis was wide-spread and mild to severe in nature. One 10% cotton linters female displayed a fibroadenoma of the mammary gland. Since the authors found no apparent relationship between NC feeding and the incidence or severity of any of these lesions, histologic data for low and middle dose rats were not evaluated and the necropsy after one month of recovery was omitted.

It was further reported that in rats treated for 24 months, there were no statistically significant differences in absolute and relative organ weights between treatment groups or when compared to controls. Upon histopathologic examination, a large number of lesions were found in various tissues of rats fed NC for 24 months without a recovery period but none were reported to be

significantly different from controls. Some lesions, such as chronic murine pneumonia, were found in most rats. Other lesions were found less frequently with the variety and incidence of these lesions attributed to being typical of geriatric rats. The lesions included bile duct hyperplasia, foci or areas of hepatocellular alteration, testicular degeneration and/or atrophy, senile nephropathy, nephritis or focal tubular nephrosis and mammary gland fibroadenoma, adenoma or adenocarcinoma. Hemosiderosis and/or extramedullary hematopoiesis of the spleen occurred almost twice as frequently in females than in males while myocardial degeneration and/or fibrosis were twice as frequent in males. No lesions were reported to be related, in incidence or severity, to the NC dose administered. Similarly, lesions from rats fed NC for 24 months and allowed to recover for 1 month were not considered to be NC-related. Also, in rats dying before the scheduled termination of the experiment (averaging between 40% to 45% in males and females, respectively), there were no NC-related lesions reported. The cause of these early deaths was not addressed by the authors.

Ellis et al. (1980) also studied the effects of NC administration in male and female mice (CD-1 strain; 58/sex/group) at 1%, 3% or 10% in the feed on a dry weight basis for up to 24 months employing procedures similar to those used for dogs and rats. Controls received either 10% cotton linters in the diet or regular chow. (Ref. Table A1-1: Using the authors' data for average terminal body weight at 24 months and the average consumption over 24 months [mean of 18 monthly measurements; measurements for months 4 to 7 were omitted due to excessive scattering of feed at all levels], these doses correspond to approximately 1,814 and 4,866 mg/kg/day at 1% and 3%, respectively, for males and 1,767 and 6,056 mg/kg/day, respectively, for females). As in the rat study previously described, the actual intake of 10% NC or 10% cotton linters in the diet could not be calculated with any degree of accuracy due to what was described as an excessive scattering of the fibers.

As reported in the previous study by Ellis et al. (1976), some early deaths (in the first 3 weeks of the study) due to intestinal impaction by the fibrous material also occurred in mice fed the high dose (10%) of NC and cotton control (10% linters) for up to 24 months. Gross necropsy found emboli of white fibrous material blocking the intestines at various sites from the jejunum downward. Additional mice, fed the respective diets from the start of the study, were substituted for the dead mice.

The high fiber content of the 10% diets (cotton linters and NC) was also reported as the probable cause of an apparent irritation effect in these animals that first occurred in week 18 and decreased by the end of month 10. This effect was characterized by hyperemia of the ears and eyelids, and subsequent edema of the genitalia, feet and tail accompanied by continued scratching. This effect was not correlated with any other toxic sign and was almost non-existent in the lower treatment levels and untreated controls. The effect was, therefore, attributed to the physical, not chemical, nature of the diet.

In mice fed NC for 12 months, the only statistical differences among the treatment groups (4/sex/level) were significant increases in weight of the spleen and ovaries, both absolute and relative to body and brain weight, in the cotton control females. Since similar increases were not seen at other necropsies nor were pathological lesions found, these increases were presumed by the authors to be normal variations, unrelated to treatment. Animals fed the 10% diets (NC or linters) lost weight during the first week of the study but quickly began to gain, leveling off by 4 months, with average weights of all dosage groups converging during the second year. Upon histologic examination, male and female mice fed NC at all levels for 12 months showed a variety of lesions, usually degenerative or inflammatory. As is commonly seen in older mice, widespread amyloidosis of most tissues was observed, with deposits most heavily concentrated in the intestine and kidney. However, the authors indicated there was no consistent relationship between any of the lesions and the NC treatment. Also, no treatment-related variations in the results of routine hematologic parameters, SGPT or BUN, were reported.

In mice fed NC for 24 months with or without a recovery period, there were no treatment-related differences in organ weights, routine hematologic parameters, SGOT, SGPT nor BUN. Tissue lesions were found in mice fed the untreated control diet or high (10%) NC dose and sacrificed after 24 months feeding, as well as in those animals dying before that time. A variety of lesions, usually degenerative, were seen. Amyloid deposits, often heavy, were widespread. These were not reported to be related to NC exposure. No histologic data were provided for control mice fed 10% cotton linters. Due to a lack of treatment related effects, no histologic data were provided for mice fed NC at 1% and 3%; nor were these data provided for treated mice allowed to recover for one month following NC treatment.

At about month 9, many deaths (approximately 25% of the original number) with no apparent cause occurred in the high dose mice with a smaller number occurring in the cotton controls. A physical fiber effect was considered; however, since the death rate was three times higher in the NC-treated mice, the authors felt that a compound effect of unknown mechanism could not be dismissed. Rapid autolysis characteristic of mice precluded histopathological examination.

C. Genetic Toxicology

Studies have been conducted to determine the mutagenic potential of nitrocellulose employing bacterial assays as well as cytogenetic tests. Mutagenic activity was not detected using these bioassay systems under conditions of the tests.

Ellis et al. (1978) conducted an Ames test exposing S. typhimurium tester strains TA1535, TA1537, TA1538, TA98 and TA100 to nitrocellulose at 100, 1,000 or 5,000 micrograms/plate for 48 hours. No statistically significant increase in the number of revertant colonies was observed when compared to levels of spontaneous revertants either with or without S9 metabolic activation (added rodent liver homogenate).

Ellis et al. (1976) studied the cytogenetic effects of NC on somatic cell chromosomes employing peripheral blood lymphocyte and kidney cultures from rats fed NC at 10% (mg/kg intake cannot be calculated due to excessive scattering of fibers) for 13 weeks. Treated rats did not show any changes in chromosome frequency distribution, number of tetraploids, or frequency of chromatid breaks, gaps or translocation in the test cultures when compared to cotton control (10% linters) cultures. No data on untreated controls was available for comparison. Ellis et al. (1980) reported that kidney and bone marrow cells from rats exposed to NC or cotton linters in the diet at 10% (exact dose not calculated due to excessive scattering) for 2 years showed no numerical or morphological changes in chromosomes.

D. Carcinogenicity

Long-term studies conducted in dogs, rats and mice indicated that the administration of NC in the diet for up to 24 months did not significantly affect the incidence of tumors in various organs/systems in dogs, rats and mice when compared to control animals.

Ellis et al. (1980) conducted 12 or 24 month feeding studies to determine the incidence of tumor formation following exposure to NC at up to 10% in the diets of dogs, rats and mice. The studies described below are the same as those described under "Lifetime Exposure" and are discussed more fully therein.

Beagle dogs (6/sex/dose) were administered 1%, 3% or 10% NC (Ref. Table A1-1: These doses correspond to approximately 311, 1,013 and 4,070 mg/kg/day, respectively, for males and 344, 1,034 and 4,576 mg/kg/day, respectively, for females, as described under Lifetime Exposure) for 12 to 24 months. Two additional groups were run concurrently for each sex and either remained untreated or received 10% cotton linters in their diets. Following treatment, the animals were sacrificed and tissues were examined for occurrence of tumors in various organ systems. The authors reported no biologic variations or tumors in the test dogs.

Rats, 32/sex/dose, were fed NC for up to 24 months at 1%, 3% or 10% in the diet (Ellis et al., 1980). (Ref. Table A1-1: These levels correspond to approximately 350 and 1,280 mg/kg/day for 1% and 3%, respectively, in males and 373 and 1,422 mg/kg/day, respectively, in females. Intakes for the 10% level could not be calculated.) Two additional groups were run concurrently for each sex and either were untreated or received 10% cotton linters. Following treatment, the animals were sacrificed and evaluated histologically for tumor formation in various organ systems.

The authors reported the occurrence of pituitary chromophobe cell adenomas and various mammary tumors, including fibroadenomas, adenomas, and adenocarcinomas/carcinomas at all dose levels. These tumors also occurred in untreated and cotton controls. There was a scattered incidence of many other

naturally occurring tumor types in rats in all treatment and control groups. The lesions found in various organ systems in NC-treated rats were attributed by the authors to nitrocellulose.

Ellis et al. (1980) also fed three groups of CD-1 mice (58/sex/group) NC at 1%, 3% or 10% as dry weight in the feed for up to 24 months. (Ref. Table A1-1: These levels correspond to approximately 1,814 and 4,866 mg/kg/day at 1% and 3%, respectively, for males and 1,767 and 6,056 mg/kg/day, respectively, for females. Intake for the 10% level could not be calculated.) Two additional groups were run concurrently for each sex and either were untreated or received 10% cotton linters. At the end of the treatment period, the control and treated mice were sacrificed and tissues were examined for occurrence of tumors in various organ systems.

The authors reported the occurrence of bronchioalveolar carcinomas in control animals, but none were observed in mice administered 10% NC for 24 months. The absence of such tumors was statistically significant in males but not in females ($P = 0.004$ for males, $P = 0.29$ for females, $P = 0.002$ for the combined sexes, by exact analysis of the contingency table). However, the authors concluded that the difference probably represents natural variation and is toxicologically meaningless. The slides from other dosage groups were not examined.

E. Reproductive Effects

Three-generation studies in rats indicated that NC administered alone in the diet at dose levels up to 10% did not adversely affect reproduction. However, the increased inert bulk of 10% fibers (NC or linters) may reduce the lactation index and pup weight.

Ellis et al. (1980) administered nitrocellulose in the diet of rats at 1%, 3% or 10% in a three-generation study. (Ref. Table A1-1: These doses correspond to approximately 350 and 1,280 mg/kg/day for 1% and 3%, respectively, in males and 373 and 1,422 mg/kg/day, respectively, for females. The actual intake for the 10% dose level cannot be calculated.) The initial groups of rats used as the parental (F_0) generations were started at the same time as the chronic study. Rats of each subsequent group, parents and offspring, received the same control or NC-containing diets as their original F_0 generation. First mating occurred when rats were 8 months of age. Following treatment, all offspring were examined at birth for gross physical abnormalities and the numbers of live and dead pups of each litter were recorded. Survival and body weights were recorded at 0, 4 and 21 days. Reproductive performance for each parental and offspring generation was determined.

The authors reported that the mean body weights at the time of first matings for males of all parental generations given diets containing 10% NC were significantly reduced when compared to males given untreated control diet. This reduction in body weight was also significant in males and females fed cotton control (10% linters) diets.

There were no indications that the treatments adversely affected the fertility of the males or females in the mating or pregnancy ratios. For the F_0 generation, most of these parameters actually suggested that either 10% NC or 10% cotton linters in the diet increased the fertility of rats given these treatments. However, this effect appears to be caused by the decreased fertility of the control F_0 females. The fertility of the F_0 females was similar to that of controls for groups given 1% and 3% NC (approximately 373 and 1,422 mg/kg/day). This decreased fertility in the F_0 control and low dose groups was attributed by the authors to both the age at time of first mating (8 months for all F_0 parental generations) and body weights greater than that expected to give optimal reproductive performance.

No treatment-related effects were apparent at any dose or in any generation on litter size, liveborn index, birth weight, viability index, or the ratio of males to total offspring. Significant reductions in the lactation index and the weight of pups at weaning occurred with 10% NC and 10% cotton linter controls. Reductions in these parameters were observed chiefly with the F_{1b} through F_{2b} litters for both groups but were not observed with the subsequent litters. The authors attributed these reductions during lactation to relatively large amounts of inert bulk in a diet of 10% fibers (NC or linters).

F. Teratogenicity

Ellis et al, (1980) did not report conducting teratology studies.

G. Immunologic Effects

Ellis et al. (1976) studied the potential adverse effects of NC exposure on the immunologic response based on serum concentration of immunoglobulin (IgE) measured by the immunodiffusion technique of Mancini et al. (1964). The administration of 10% NC in the feed to dogs or rats (this dietary level can be calculated, as described under Thirteen-Week Studies, to correspond to an average of approximately 7,690 mg/kg/day for dogs but could not be calculated for rats due to excessive scattering of fibers) for up to 13 weeks did not alter their serum concentrations of IgE.

VI. HEALTH ADVISORY DEVELOPMENT

Nitrocellulose, at doses averaging 4,300 mg/kg/day in dogs and in excess of approximately 1,400 mg/kg/day in rats and 6,000 mg/kg/day in mice, was not toxic when fed for up to 24 months. The actual intakes in mg/kg/day in rats and mice fed 10% NC could not be determined with any degree of accuracy due to visible scattering of the fibers around the cage. Assuming, however, that these animals consumed only twice the amount of NC as those receiving the 3% diet, a reasonably conservative estimate, intake would be, at a minimum, approximately 2,800 mg/kg/day in rats and 12,000 mg/kg/day in mice. The only treatment-related effects in these high-dose, long-term feeding studies were early weight loss in rats and mice and subsequent lower average body weights in the mature rat, hyperemia with edema of the ears, eyelids, genitalia, feet and tail apparently due to physical-mechanical effects of the fibers and death due to intestinal impaction in mice fed the 10% diets (NC and cotton linters).

The weight effect was attributed to the non-nutritive bulk of the fibrous diet and was confirmed by similar findings in control animals fed 10% cotton linters (cellulose linters), the material that is nitrated to form NC. This lower body weight, however, is not necessarily an adverse effect as the rodents fed the 10% diets were characterized by less fat, not less lean body mass, when compared to untreated animals of the same species. This condition can, however, be detrimental if there is a very high body demand for nutrients, as during pregnancy and lactation. This condition occurred, to some degree, in the early litters of the three-generation reproduction study in rats, as evidenced by a decreased lactation index and weight at weaning, but not in later generations, possibly indicating adaptation.

The hyperemia with edema that occurred in mice was not life-threatening, resolved spontaneously and was of unknown cause. As this effect occurred in mice fed either 10% NC or cotton linters and was accompanied by continuous scratching, a direct physical effect due to irritation from contact with the fibers seems likely.

The deaths due to intestinal impaction were attributed to the relatively large size of the fibers in relation to the size of the lumen of the intestines, allowing the masses formed by the fibers to completely obstruct the gut. This effect occurred in mice fed both the 10% NC and cotton linters. Unresolved is a spate of deaths of unknown cause that occurred at 9 months in both the 10% NC and cotton linters groups but was at a higher level in the NC group. This may be due, in part, to the chemical nature of NC.

In 13-week feeding studies at the same levels, intakes averaged 7,700 mg/kg/day in dogs and were in excess of approximately 2,700 mg/kg/day in rats and 7,000 mg/kg/day in mice. Calculation of the 10% levels to approximates, as in the long-term study, would yield values, at a minimum, of 5,400 mg/kg/day in rats and 14,000 mg/kg/day in mice. There was no evidence of toxicity. The increased food

consumption/decreased weight gain pattern in rats and mice was similar to that in the 24-month study, occurred at the 10% level in animals fed either NC or cotton linters and was attributed to the non-nutritive bulk of the fibers.

Death due to intestinal impaction also occurred in the high-dosed mice in this study and was attributed to the physical nature of the fibers. Since the treated animals, like humans, cannot digest cellulose, passage of these fibers through the digestive tract would be expected.

This non-digestion of the fibrous diet was confirmed in absorption studies. After repeated oral doses (once daily for four days) of radiolabelled nitrocellulose to rats, no detectable radioactivity was found in any tissue or body fluid but was recovered only from various components of the GI tract, contents and feces.

Nitrocellulose was not mutagenic in either bacterial bioassays nor did it produce chromosome abnormalities in mammalian cells after in vivo exposure. It did not significantly affect tumor incidence in dogs, rats and mice and produced only some adverse effects in rats with high nutrient requirements during pregnancy and lactation.

In view of the non-toxic nature of NC at all doses studied and its failure to be digested and absorbed in the species tested, health advisory (HA) values for 1-Day, 10-Days and Longer-term appear to be unnecessary. It seems probable that, due to the fibrous nature of the substance and its insolubility in water, clarity or turbidity of the water would be the only guideline necessary.

VII. ANALYSIS

Rosenblatt et al. (1973) in summarizing literature on the analysis of NC indicated that all analytical procedures probably would begin with collection of NC fibers from the water on filters. Weighing the filter is cited as a method to roughly estimate NC, but its accuracy would be limited by the presence of inert solids.

Other methods cited include:

- Ferrous-titanous titration
- Ferrous sulfate titration
- Liberation of NO_2 gas
- Analysis of NH_3 after reduction by Devarda's alloy
- Transnitration of salicylate or citrate followed by ferrous-titanous titration
- Chromous chloride-ferric ammonium sulfate micro-determination
- Zinc dust reduction of the nitrate ester
- Hydrolytic liberation of nitrite ion in acetone

Of the detection methods listed above, the last one is considered to be the most effective for detecting low levels of NC in the environment (Sullivan et al., 1978; Rosenblatt et al., 1973). It is a colorimetric method based on hydrolytic liberation of nitrite by OH^- from acetone solutions of nitrate esters. The resulting NO_2^- is then diazotized with either alpha-(naphthyl)-ethylenediamine hydrochloride or alpha-naphthylamine and the absorbance of the solution determined at 520 to 530 nm. The reaction is not specific for NC; however, the insolubility of this compound in water allows quantitative separation from NO_2^-, NO_3^-, and other soluble nitrate esters or nitrocompounds in mixed wastewater by filtration or dialysis. Barkley and Rosenblatt (1978) adapted this procedure to the Technicon Autoanalyzer. The procedure involves aspiration of a stirred NC suspension, dialysis against 9% saline, and hydrolysis with 5N NaOH at 70° C for 10 minutes to release nitrite ion. Sulfanilic acid is diazotized by the nitrite ion at low pH. The resulting diazonium salt is coupled with the N-(1-naphthyl)ethylenediamine, and the color produced is measured at 520 nm. The limit of detectability is 0.4 mg/L of nitrocellulose.

Sullivan et al.(1978) outlined two methods for determining NC in sediment. The first method involves solvent extraction of the dried sediment in acetone or ethylacetate. The procedure is sensitive to as little as 0.5 mg/kg of nitrate ester; however, it is not specific for NC because it also extracts other organic nitrate esters and nitrocompounds. The second method involves an initial acetone extraction to remove the nitrate ester. Nitrate is then determined colorimetrically since it will oxidize ferrous iron to ferric iron after treating the extract with acetic acid, ferrous sulfate in sulfuric acid, and sodium sulfite. Absorbance of the resulting yellow color is determined at 500 nm. This procedure, however, lacks sensitivity since the minimum detectable concentration in a 10 g sediment sample is 140 mg/kg.

VIII. TREATMENT

Wastewater from NC production facilities is neutralized, then settled, centrifuged, and/or screened to recover NC fibers (Sullivan et al., 1978). Centrifugation leads to more efficient and constant recovery due to the high specific gravity of NC (Rosenblatt et al., 1973).

The US Army Natick Laboratories (Massachusetts) has developed a chemical and microbiological process for the degradation of NC in wastewater (Rosenblatt et al., 1973). The process involves membrane ultrafiltration of the wastewater to concentrate the suspended NC. A 200-fold concentration, to a 3% to 5% NC suspension, was desired; however, only a 10-fold concentration, to 0.2% NC, has been obtained by this process. The suspension is then treated with 3% NaOH at 90° to 95° C for 20 minutes to yield a soluble material containing little nitrate ester. After acid neutralization, nitrate ester content of the filtrate is determined by IR analysis. An extract of the filter is similarly analyzed to detect any undissolved nitrate ester, presumably NC. The neutralized solution is mixed with domestic waste and fermented anaerobically to denitrify thus producing gaseous nitrogen as a product. Methanol could be added as a nutrient in this step. The next step is an aerobic activated sludge treatment and finally, a second denitrification, again using methanol nutrient. The final product was reported to be nitrocellulose free.

IX. CONCLUSIONS AND RECOMMENDATIONS

Based on available toxicity data and the chemical and physical properties of the compound, NC is apparently non-toxic to dogs, rats and mice and is not digested nor absorbed in these species. These data, along with the relative insolubility of NC in water, suggest that Health Advisory values for NC in drinking water are unnecessary. The physical characteristics of the drinking water as they relate to turbidity, clarity, taste and similar indicators of palatability appear to be the only guidelines necessary.

A companion report, "Data Deficiences/Problem Areas and Recommendations for Additional Data Base Development For Nitrocellulose" (Appendix 2) summarizes the scope and adequacy of existing data reviewed for this HA and delineates those areas where additional data, if any, are deemed necessary.

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APPENDIX 1

CALCULATION METHODS

TABLE A1-1

Calculation of Intake of Test Material (mg/kg/day)

$$\text{Intake} = \frac{(a)(b)(1000)}{(100)(c)}$$

where:

a = % NC in diet

b = intake of feed in grams/day*

1000 = conversion factor, grams to milligrams

100 = conversion factor, % to grams/100 grams

c = animal weight in kilograms*

*Intake/animal weight data used may vary for each calculation depending upon information available in report. Text will describe exact conditions for determining these calculations for each experiment.

APPENDIX 2

DATA DEFICIENCIES/PROBLEM AREAS AND RECOMMENDATIONS FOR ADDITIONAL DATA BASE DEVELOPMENT FOR NITROCELLULOSE

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INTRODUCTION

The Office of Drinking Water (ODW), Environmental Protection Agency (EPA), in conjunction with the Department of the Army, has reviewed the available data on nitrocellulose (NC) for the purpose of developing a Health Advisory (HA) useful in dealing with contamination of drinking water, to include "state-of-the-art" information on health effects, analytical methodology and treatment technology. This information is contained in detail in the report entitled "Health Advisory on Nitrocellulose."

OBJECTIVES

The objective of this document is to provide an evaluation of data deficiencies and/or problem areas encountered in the review process for NC and to make recommendations, as appropriate, for additional data base development. This document is presented as an independent analysis of the current status of NC toxicology, as related to its possible presence in drinking water, and includes a summary of the background information used in the development of the HA. For greater detail on the toxicology of NC, the original "Health Advisory on Nitrocellulose" should be consulted.

BACKGROUND

Nitrocellulose is a non-volatile, fibrous, cotton-like, white solid used as a principal ingredient of propellants, smokeless powder, rocket fuel, mortar increments and some explosives (Sullivan et al., 1978). It is produced for military use at selected Army ammunition plants (AAP), and NC fines are found in production wastewater (Huff et al., 1975). It is resistant to biological degradation and is, therefore, persistent in the environment and deemed a potential, if not known, contaminant in drinking water.

The metabolism of NC as studied in rats (Ellis et al., 1976) indicated that the compound remained in the gastrointestinal (GI) tract and was excreted unchanged.

Acute toxicity studies in rats and mice (Lee et al., 1975) indicated that NC was nontoxic, with LD_{50} values greater than 5,000 mg/kg reported in both species.

Thirteen-week (Ellis et al., 1976) and 24-month (Ellis et al., 1980) feeding studies in three species (dogs, rats and mice) gave no evidence of adverse or toxic effects related to the chemical characteristics of NC; nor was NC found to be carcinogenic. The fibrous physical nature of NC, however, was the cause of early deaths due to intestinal impaction in mice fed 10% NC or cotton linters in both the 13-week and 24-month studies and was associated with an increased food intake-decreased weight gain pattern in high dosed and cotton control rats and mice. The fibers were also reported to be the cause of a physical irritation of the extremities of mice fed 10% NC or cotton linters as evidenced by hyperemia and

edema. A spate of deaths of unknown cause occurred in mice after nine months of feeding NC or cotton linters at 10% in the diet. The number of deaths was higher in the NC treated mice and may, therefore, be related to the chemical nature of the compound via a mechanism, as yet, undetermined (Ellis et al., 1980).

Nitrocellulose was reported to be non-mutagenic in various indicator systems (Ellis et al., 1976, 1978, 1980). Three-generation reproduction studies in rats indicated that NC did not adversely effect reproduction but that the non-nutritive bulk of the 10% diet may cause an adverse effect during periods of high nutritional demand, such as pregnancy or lactation, as evidenced by a decrease in lactation index and weight at weaning (Ellis et al., 1980).

No teratogenic studies were reported. Exposure to NC did not affect the immunological response of dogs or rats (Ellis et al., 1976).

Methods of analysis (Barkley and Rosenblatt, 1978) and treatment (Rosenblatt et al., 1973) adequate for detection and removal of NC at levels which might be deemed hazardous to health have been presented in detail in "Health Advisory on Nitrocellulose."

The lack of toxicological indicators, along with the apparent non-absorption/non-digestion of the NC fibers, led to the conclusion that HA values for NC in drinking water were unnecessary.

DISCUSSION

Available data on the pharmacokinetics, health effects, analysis and NC wastewater treatment have been reviewed.

While the available data on the metabolism of NC are limited in scope, the chemical and physical nature of NC generally supports the finding of the one available study that NC passes through the GI tract apparently unchanged and unabsorbed. Additional studies would, therefore, be unnecessary.

The available studies on the toxicity of NC include LD_{50}'s in rats and mice and short-term (13 week) and longer-term (24 month) studies in dogs, rats and mice that included assessments for possible carcinogenicity. Three-generation reproduction studies in rats, mutagenicity assays in bacterial and cytogenetic systems and immunological studies in dogs and rats have also been reported. All studies appear adequate for use in HA development.

Further investigation of the cause of the spate of deaths in mice occurring at nine months in the longer-term feeding study seem warranted but, in view of the otherwise low toxicity of NC along with the other available data, would not be necessary for HA development. Teratogenic studies were not reported; however, the apparent inability of NC to be absorbed would preclude its acting as a potential teratogen. Therefore, additional studies seem unnecessary at this time.

Primary skin and eye irritation tests in rabbits were negative (Lee et al., 1975). However, mice fed 10% NC or cotton linters for up to 24 months developed edema and hyperemia of the extremities, apparently due to the fibrous nature of NC. More sensitive dermal studies, if available, would be appropriate but would not be deemed necessary as regards contamination of the drinking water by NC.

Several methods of analysis of NC in wastewater have been reported including a method adapted to the Technicon Autoanalyzer. The limit of detectability, 0.4 mg/L, appears adequate for determining drinking water contamination relative to palatability concerns.

Methods for the treatment of wastewater by chemical and microbiological degradation have been developed. The insolubility of NC in water and its ability to be removed by coagulation and/or filtration make it unlikely that more extensive treatment measures would be required.

CONCLUSIONS/RECOMMENDATIONS

Based on the above discussion, the following conclusions/recommendations can be made:

1. The available studies on NC toxicity are adequate for development of a HA useful in dealing with contamination of drinking water.

2. No significant data gaps or problem areas relative to NC in drinking water exist.

3. No further studies on NC, as relates to its possible presence in drinking water, are necessary at this time.

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