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Provisional Peer-Reviewed Toxicity Values for

Nitrocellulose
(CASRN 9004-70-0)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR NITROCELLULOSE (CASRN 9004-70-0)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

No RfD, RfC, or carcinogenicity assessment for nitrocellulose is available on IRIS (U.S. EPA, 2008) or the Health and Environmental Assessment Summary Tables (HEAST; U.S. EPA, 1997). Nitrocellulose is not included in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994). The Drinking Water Standards and Health Advisories list (U.S. EPA, 2006) does include nitrocellulose, but it notes that the Health Advisory Document (HA) for nitrocellulose (U.S. EPA, 1987) does not include HA values and describes this compound as relatively nontoxic. The HA was developed under a cooperative agreement between U.S. EPA and the U.S. Army (Roberts, 1985) and is also presented by Hartley et al. (1992). The U.S. Army also developed a Water Quality Criteria for Nitrocellulose (Ryon, 1986). The Agency for Toxic Substances and Disease Registry (ATSDR, 2008) has not produced a Toxicological Profile for nitrocellulose, and no Environmental Health Criteria Document is available from the World Health Organization (WHO, 2008). The American Conference of Governmental Industrial Hygienists (ACGIH, 2007), the Occupational Safety and Health Administration (OSHA, 2008), and the National Institute for Occupational Safety and Health (NIOSH, 2008) have not established occupational health standards for nitrocellulose. The carcinogenicity of nitrocellulose has not been assessed by the International Agency for Research on Cancer (IARC, 2008) or the National Toxicology Program (NTP, 2005, 2008).

Literature searches were conducted from the 1960s through May 2009 for studies relevant to the derivation of provisional toxicity values for nitrocellulose. Databases searched include DTIC, MEDLINE, TOXLINE (Special), BIOSIS, TSCATS/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents.

REVIEW OF PERTINENT DATA

Human Studies

A retrospective cohort study examined mortality among 2490 males who worked in a Massachusetts plastics producing plant for at least 1 year during 1949−1966 (Marsh, 1983). Chemicals produced in this plant included nitrocellulose (cellulose nitrate), cellulose acetate, styrene polymers, polyvinyl chloride, polyvinyl butyral and phenolic and melamine resins. Vital status was determined as of December 31, 1976, for 99.7% of the cohort, and death certificates were obtained for 98.0% of 603 observed deaths. Comparison with local county white males revealed a slight excess in mortality from digestive-system cancer (standardized mortality ratio [SMR] = 101.8, CI not reported) and a statistically significant excess ($p < 0.05$) in genitourinary cancer (SMR = 153.6, CI not reported). A secondary (nested) matched case-control study was conducted to determine if particular jobs or work areas were related to the excesses found in the primary study. For nitrocellulose processing, the odds ratios for all digestive-system cancers combined were 1.07, 1.91, and 2.85 for exposures greater than 1 month, 5 years, and 10 years, respectively; none of these odd ratios were statistically significant. For specific digestive system cancers, a statistically significant ($p < 0.05$) odds ratio of 8.90 was found based on four cases of rectal cancer among workers employed in cellulose nitrate production for periods greater than 5 years. These findings are only weakly suggestive of a possible association between cellulose nitrate production and rectal cancer due to concurrent multiple chemical exposures, small number of deaths and other study limitations.

Animal Studies

Oral Exposure, Subchronic Duration

Ellis et al. (1976) conducted 13-week oral toxicity studies of nitrocellulose in rats, mice, and dogs. These studies used a common exposure protocol with three treatment groups and two control groups for each species. The treatment groups received 1, 3, or 10% nitrocellulose in the feed calculated on a dry-weight basis. There were two control groups receiving either untreated feed (normal controls), or feed containing 10% cotton linters ([cotton controls] cellulose linters [short-fibered cotton hairs], the material that was nitrated to produce the nitrocellulose) to determine if any observed effects were due to the passage of nonnutritive bulk through the gastrointestinal tract.

The 13-week study with young CD rats used groups containing eight males and eight females (Ellis et al., 1976). Using average feed intake data over Weeks 1−13 and average body weights from Weeks 0, 4, 8, and 13, U.S. EPA (1987) calculated that doses for the 1 and 3% nitrocellulose groups were approximately 667 and 2366 mg/kg-day for males and 820 and 2673 mg/kg-day for females. Measured intakes for the rats fed 10% nitrocellulose or 10% cotton linters in the diet were more than double those of the untreated control rats. At 10% nitrocellulose or 10% cotton linters in the diet, enormous mounds (unquantified) of white fluffy material were scattered all around the cages. Therefore, actual intake of nitrocellulose or cotton linters at 10% in the diet cannot be calculated with any degree of accuracy (U.S. EPA, 1987).

Evaluations in all groups of rats included behavioral changes and toxic signs (daily), body weight (weekly), hematology (Weeks 4, 8, and 13) and clinical chemistry (Week 13) (Ellis et al., 1976). Hematological endpoints included erythrocyte, leukocyte, reticulocyte, and

platelet counts, hemoglobin parameters, and mean corpuscular volume among other standard measures. Clinical chemistry endpoints included blood glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, lactate dehydrogenase, α-hydroxybutyrate dehydrogenase, and creatine phosphokinase. Rats fed 10% nitrocellulose or 10% cotton linters for 13 weeks were also evaluated for serum immunoglobulin E (IgE) concentration and chromosomal aberrations in lymphocytes and kidney cells. After 13 weeks, four males and four females from each group were necropsied for evaluation of organ weights (liver, kidneys, spleen, testes, ovaries, and brain), gross pathology, and histopathology (comprehensive; rats fed 1% or 3% nitrocellulose or 1% or 3% cotton linters not examined). Treatment for the remaining animals in each group was discontinued, and they were maintained for an additional 4 weeks to evaluate the reversibility of any adverse effects. These animals were not necropsied or evaluated for hematology and clinical chemistry because there were no adverse effects on these endpoints in the animals evaluated at 13 weeks. Specific results for animals fed 1% or 3% cotton linters were not reported.

Body-weight gain was reduced in the male rats fed 10% nitrocellulose or 10% cotton linters (body weight after 13 weeks of exposure was 14−17% and 21−22% less than unexposed controls, respectively) (Ellis et al., 1976). Food consumption was slightly increased in both sexes at 1 and 3% nitrocellulose. Male and female rats fed 10% nitrocellulose or 10% cotton linters consumed large amounts of feed, but they scattered much of it around the cages. These rats apparently tried to discard the fiber while trying to get at the feed. The authors concluded that the reduced weight gain in the male rats occurred because they did not absorb enough of the nutritive portion of the feed. There was no apparent increase in feed scattering in the groups fed the lower dietary concentrations of nitrocellulose, indicating that these rats ate more feed to compensate for the nonnutritive fiber in their diet; the rats apparently received enough nutritional intake from their increased intake because they gained weight comparably to the untreated controls. Nitrocellulose administration did not cause any significant hematology or clinical chemistry changes or any gross or microscopic lesions. The male rats fed 10% nitrocellulose or cotton linters had absolute liver, kidney, and/or spleen weights that were significantly lower than the untreated control males. The authors attributed these changes to the depressed body-weight gain because the relative weights of these organs based on body weight and brain weight were comparable to those of the untreated controls. Based on the lack of systemic effects, this study identified a NOAEL of 3% nitrocellulose (2366 mg/kg-day). The decrease in body weight at the high dose of 10% nitrocellulose is not relevant for humans because of the lack of relevance of the mode of action (MOA; decreased nutritional intake by physical interference).

The 13-week study with young albino Swiss mice had groups containing eight males and eight females (Ellis et al., 1976). Using average feed intake data over Weeks 1−13 and average body weights from Weeks 0, 4, 8, and 13, U.S. EPA (1987) calculated that doses for the 1 and 3% nitrocellulose groups were approximately 1690 and 5062 mg/kg-day for males and 1741 and 7000 mg/kg-day for females. As in the rat study, the actual intake of 10% nitrocellulose or 10% cotton linters in the diet cannot be calculated with any degree of accuracy due to excessive scattering of the fibers (U.S. EPA, 1987). Evaluations were similar to those described for the rats except that clinical chemistry, serum IgE, and cytogenicity were not assessed in the mice. After 13 weeks, four males and four females from each group were necropsied for evaluation of organ weights (liver, kidneys, spleen, testes, ovaries, and brain), gross pathology, and histopathology (comprehensive; mice fed 1% or 3% nitrocellulose not examined). Treatment for the remaining animals in each group was discontinued, and they were maintained for an

additional 4 weeks to evaluate the reversibility of any adverse effects. These animals were not necropsied or evaluated for hematological changes because there were no adverse effects on these endpoints in the animals evaluated at 13 weeks.

The main effects in the mice were weight loss and deaths during the first few weeks of the study in males and females fed 10% nitrocellulose or cotton linters (Ellis et al., 1976). The deaths were apparently due to intestinal impaction from the fibrous physical nature of the substances as the lower part of the intestinal tract was blocked by masses of fibers. (The authors noted that the rats did not experience these deaths because their intestines were probably sufficiently large, relative to fiber length, to allow continued passage of fiber.) Additional mice from a chronic study (same shipment and identical levels of nitrocellulose) were added to this study to compensate for the early losses. The surviving 10% nitrocellulose mice gained weight; some had come close to the normal control weight by Week 13. The body weights of the mice fed 1 or 3% nitrocellulose were similar to those of the normal controls. The mice fed 1 or 3% nitrocellulose consumed slightly more feed than the controls. Feed consumption in the mice fed 10% nitrocellulose or 10% cotton linters was considerably higher; as in the rats, this reflected scattering of fibers and feed about the cages. There were no consistent or toxicologically significant hematological changes in any of the groups. Absolute and/or relative spleen weights of mice fed 10% nitrocellulose or cotton linters were significantly smaller than those of the normal control mice. No treatment-related gross or histopathologic changes were observed in the surviving mice. This study identified a NOAEL of 3% nitrocellulose (5062 mg/kg-day in males and 7000 mg/kg-day in females). The mortality and weight loss at the high concentration of 10% nitrocellulose is discounted as a concern for humans because of the nature of the physical blockage of the intestinal tract. The effects were similar to those found in the cotton controls.

The 13-week study with young beagle dogs used groups containing two males and two females (Ellis et al., 1976). There were three treated groups that were fed nitrocellulose at 1, 3, or 10% in the feed as dry weight. Using average feed intake data for Weeks 1−4 (data for Weeks 5−13 not reported) and data for body weight at Week 4, U.S. EPA (1987) calculated that the doses for the 1, 3, and 10% nitrocellulose groups were approximately 518, 1900, and 6890 mg/kg-day for males and 610, 2976, and 8485 mg/kg-day for females. The doses for the 10% cotton-cellulose linters group were similarly calculated to be approximately 6181 mg/kg-day in males and 8627 mg/kg-day in females. The evaluations were similar to those of the rats except that the clotting time and bromsulfophthalein (BSP) retention tests were also performed and cytogenicity was not assessed. After 13 weeks, one male and one female from each group was necropsied for evaluation of organ weights (liver, kidneys, spleen, testes, ovaries, and brain), gross pathology and histopathology (comprehensive; dogs fed 1% or 3% nitrocellulose not examined). No adverse effects were observed in the dogs fed nitrocellulose or cotton linters. Food consumption was increased in all treated dogs and was approximately 15% higher than the normal controls in those fed 10% nitrocellulose or cotton linters. The authors indicated that the net food consumption by all dogs was similar if it is assumed that the nitrocellulose and cotton linters were nonnutritive bulk. All dogs, including the untreated controls, showed some variations in body weight and hematology and clinical chemistry indices, but the changes were within normal limits. No treatment-related changes in organ weight, gross pathology or histopathology were observed. This study identified a NOAEL of 10% nitrocellulose (6890 mg/kg-day in males and 8485 mg/kg-day in females); no LOAEL was identified.

Oral Exposure, Chronic Duration

Ellis et al. (1980) conducted 24-month oral toxicity studies of nitrocellulose in rats, mice, and dogs. These studies used a common exposure protocol with three treatment groups and two control groups for each species. The treatment groups received 1, 3, or 10% nitrocellulose in the diet calculated on a dry basis. Control groups were similar to those in the Ellis et al. (1976) study (normal and cotton controls).

The 24-month study with CD rats used groups of 32 males and 32 females supplemented with additional groups of 8 males and 8 females exposed for 12 months (Ellis et al., 1980). Using average feed intake over 24 months (mean of 23 monthly measurements) and average terminal body weight at 24 months, U.S. EPA (1987) calculated that doses for the 1 and 3% nitrocellulose groups were approximately 350 and 1280 mg/kg-day for males and 373 and 1422 mg/kg-day for females. Dietary intake of nitrocellulose or cotton linters at 10% in the diet could not be estimated because of extensive food and fiber scatterings around the cages. Evaluations included clinical observations (daily), body weight (weekly for first 6 months and then biweekly), food consumption (first 4 weeks then during last week of each month), hematology (4/sex/group after 6, 12, 18, and 24 months), and clinical chemistry (4/sex/group after 12 and 24 months). Evaluated endpoints were the same as in the subchronic study (Ellis et al., 1976). Necropsies were conducted after 12 months (4/sex/group) and 24 months, as well as on rats dying at unscheduled times, for evaluation of organ weights (liver, kidneys, spleen, testes, ovaries and brain), gross pathology and histopathology (comprehensive). After 24 months of treatment, 4 rats/sex/group were given the untreated control diet for 28 days to evaluate the reversibility of any effects.

Average body weights in the rats fed 1 or 3% nitrocellulose were similar to those in the unexposed controls (Ellis et al., 1980). Rats in the 10% nitrocellulose and 10% cotton linters groups failed to gain weight or lost weight in the first week and, thereafter, gained weight more slowly than the unexposed controls, reaching plateaus after 1 year of 575−600 g in males and 325−350 g in females compared to 775 g in male controls and 375 g in female controls; the deficits from controls were reduced somewhat at the end of the study, as the high-dose rats gained weight slightly faster than controls over the second year of the study. Rats fed the 10% nitrocellulose or 10% cotton linters diets had a somewhat better survival rate than unexposed controls; the authors concluded that this was probably associated with their lower body weight, which was apparently due to decreased obesity (i.e., decreased body fat rather than decreased lean body mass). Treated rats had a dose-related increase in apparent feed consumption consistent with the fact that nitrocellulose acts as a nonnutritive bulk. Apparent feed consumption for rats given 10% nitrocellulose or 10% cotton linters was approximately twice that of untreated controls, but some of this increase was due to scattering of diet around the cages, which accounted for part of the loss of weight in the feeders (the measured parameter); the rats wasted large quantities of diet apparently attempting to remove fiber from feed. The hematology, clinical chemistry, organ weight, histopathology, and other evaluations showed normal biological variations—but no exposure-related effects. Based on a lack of systemic effects, this study identified a NOAEL of 3% nitrocellulose (1280 mg/kg-day for males and 1422 mg/kg-day for females).

The 24-month study with CD-1 mice used groups of 58 males and 58 females (Ellis et al., 1980). Based on average feed intake over 24 months (mean of 18 monthly measurements) and average terminal body weight at 24 months, U.S. EPA (1987) calculated that

doses for the 1 and 3% nitrocellulose groups were approximately 1814 and 4866 mg/kg-day for males and 1767 and 6056 mg/kg-day for females. As in the rat study, the actual intake of 10% nitrocellulose or 10% cotton linters in the diet could not be calculated with any degree of accuracy due to excessive scattering of the fibers (U.S. EPA, 1987). Evaluations were similar to those in the rat study except that blood glucose, serum alkaline phosphatase, serum IgE, and cytogenicity were not assessed in the mice. After 24 months of treatment, 4 mice/sex/group were given the untreated control diet for 28 days to evaluate the reversibility of any effects; evaluations of these mice did not include clinical chemistry or histopathology.

Effects in the mice included some early deaths during the first 3 weeks of the study in the 10% nitrocellulose and 10% cotton linters groups due to intestinal impaction by the fiber content of the feed (Ellis et al., 1980). Gross necropsy found emboli of white fibrous material blocking the intestines at various sites from the jejunum downward. Additional mice, fed the same diets from the start of the study, were substituted for the dead mice. The high fiber content of the 10% nitrocellulose and cotton linters diets was also the probable cause of an apparent physical irritation effect 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; subsequent edema of the genitalia, feet, and tail; and continued scratching (an action that implies irritation). The irritation was most common in the 10% cotton-linters group, less common in the 10% nitrocellulose group, and almost nonexistent in the other groups; it was not correlated with any other toxic sign. A large number of deaths in the 10% nitrocellulose group (approximately 25% mortality in both sexes) and a smaller number of deaths in 10% cotton-linters group occurred at approximately Month 9. Histopathological examinations were not conducted on these mice. A physical fiber effect was considered as a possible cause for the deaths because they occurred in mice fed both types of fibers, but a compound effect of unknown mechanism could not be dismissed because there were approximately three times more deaths among the 10% nitrocellulose mice than among the 10% cotton linters mice. Average body weight and apparent feed consumption in the mice fed 1 or 3% nitrocellulose were similar to those in the unexposed controls. Mice fed 10% nitrocellulose or 10% cotton linters lost weight during the first week but then began to gain; the gains leveled off after 4 months and, during the second year, the average weight of all control and treated groups converged. Apparent feed consumption for mice given 10% nitrocellulose or 10% cotton linters was approximately 2−3 times higher than that of untreated controls (consistent with the presence of nonnutritive bulk in the diet), but part of this increase was due to excessive scattering of fiber around the cages. The hematology, clinical chemistry, organ weight, histopathology and other evaluations showed no exposure-related effects. This study identified a NOAEL of 3% nitrocellulose (4866 mg/kg-day in males and 6056 mg/kg-day in females). The mortality at the high concentration of 10% is discounted as a concern for humans due to the physical nature of the effect (blockage of the intestinal tract).

The 24-month study with beagle dogs used groups of six males and six females (Ellis et al., 1980). Based on average feed intake over 24 months (mean of 22 monthly measurements) and average terminal body weight of 2 dogs/sex at 24 months, doses for the 1, 3, and 10% nitrocellulose groups were approximately 311, 1013, and 4070 mg/kg-day for males and 344, 1034, and 4576 mg/kg-day for females as calculated by U.S. EPA (1987) methodology. The approximate doses for the 10% cotton linters groups were similarly calculated to be 2888 and 3874 mg/kg-day. Evaluations included clinical observations (daily), body weight (weekly), food consumption (1 week each month), hematology (4−6/sex/group after 3, 9, 12, 18, and 24 months), clinical chemistry (same schedule as hematology), and serum IgE (same schedule as

hematology). Hematology and clinical chemistry endpoints were essentially the same as in the chronic rat study. Necropsies were conducted after 12 months (1/sex/group; 1 and 3% nitrocellulose groups not examined) and 24 months (2/sex/group) for evaluation of organ weights (same organs as in rats, as well as adrenals, thyroids and pituitary), gross pathology, and histopathology (comprehensive).

No toxic signs were observed in any of the dogs at any time (Ellis et al., 1980). There were no consistent effects on body weight although feed consumption showed a dose-related increase; the dogs fed 10% nitrocellulose or 10% cotton linters ate considerably more than the unexposed controls (average feed consumption was 28−38% and 20−22% higher, respectively). The hematology, clinical chemistry, organ weight, histopathology and other evaluations showed no exposure-related effects. This study identified a NOAEL of 10% nitrocellulose (4070 mg/kg-day in males and 4576 mg/kg-day in females); no LOAEL was identified.

Reproductive Toxicity Studies

A three-generation reproduction study of nitrocellulose was conducted in CD rats (Ellis et al., 1980). The initial groups of rats used as the parental generation (F0) were started at the same time as the previously described 24-month chronic toxicity study in rats. Rats of each group, parents and offspring of each generation, received the same control or nitrocellulose diets as in the chronic study (i.e., 0, 1, 3, or 10% nitrocellulose or 10% cotton linters). Dose estimation is precluded by insufficient feed consumption measurements (limited to the control, 10% nitrocellulose, and 10% cotton linters groups during lactation of the F2b and F3b generations) and lack of information on feed scattering. For the F0 generation, 10 males and 20 females from each group were mated after receiving the test diets for 6 months. Each male was housed with two females from the same group for 14 days. Offspring from these matings (F1a, first litters) were discarded at weaning. The F0 rats were mated a second time and 20−24 offspring of each sex from this mating (F1b, second litters) were selected from each group at weaning. The F0 females and surplus pups were discarded and the F0 males were retained in the chronic study. Each F1b male was mated with one female within the same group for 14 days at 3 months of age. The F2a generation was discarded at weaning and the F1b rats were terminated at weaning of the F2b pups. The F2b rats were then selected and mated at 3 months of age according to the same procedure used for the F1b. The study was terminated upon weaning of the F3b rats. The general health of each parental generation (F0, F1, and F2) was assessed by body weight at the first mating. At birth, all offspring were examined for gross physical abnormalities and numbers of live and dead pups in each litter were recorded. Survival and body weights were recorded at 0, 4, and 21 days. Reproductive performance for each parental generation was assessed by mating ratio (the number of copulations to number of male-female pairings), pregnancy ratio (the number of pregnancies to the number of copulations), fertility ratios for each sex (the number of males or females with offspring to the number of that sex mated) and duration of gestation. Litter indices included the litter size, the live-born index (the percentage of the total number of pups live-born), the body weight of live-born pups at birth, the viability index (the percentage of live-born pups surviving to 4 days), the lactation index (the percentage of pups alive at Day 4 surviving to weaning), the body weight of pups at weaning, and the sex ratio (the number of males to the total number of offspring).

The mean body weights at the time of first matings for males of all parental generations given 10% nitrocellulose and for males and females of all parental generations given 10% cotton linters were significantly reduced when compared to untreated controls (Ellis et al., 1980). There

were no indications that the treatments adversely affected male or female reproductive performance. Significant reductions were observed in the mean lactation index and the body weight of pups at weaning in F1b, F2a, and/or F2b litters exposed to 10% nitrocellulose and 10% cotton linters. For example, mean lactation index in the 10% nitrocellulose F2a and F2b litters was 48 and 44% lower than the respective unexposed litters. The body weights at weaning in the 10% nitrocellulose F1b, F2a, and F2b litters were 41, 45, and 32% lower than the respective unexposed litters. As in the chronic toxicity study, rats given diets containing 10% fiber (nitrocellulose or cotton linters) ate more than the other rats, presumably to compensate for the inert fiber content of the feed. The authors attributed the reductions in lactation index and pup body weight at weaning to increased fiber consumption and consequent lower maternal weight, indicating no specific nitrocellulose toxicity. This study identified a NOAEL of 3% nitrocellulose.

Other Studies

Oral absorption was studied in two CD rats that were administered four daily doses of ^{14}C-nitrocellulose by gavage (Ellis et al., 1976). The ^{14}C-nitrocellulose fibers were cut and ground small enough to fit through an 18-gauge dosing needle. One rat received the compound as a suspension in water, and the other rat received the compound as a suspension in 0.2% methyl cellulose-0.4% Tween 80 (MC-TW80). Each rat was dosed with 1 mL/100 g of either the aqueous or MC-TW80 suspension. Samples of expired CO_2, blood, urine, feces, liver, spleen, kidneys, lungs, muscle, and the gastrointestinal tract plus its contents (stomach, small intestine, cecum, and large intestine) were collected 24 hours after the last dose for analysis of radioactivity. Radioactivity was recovered only in the various parts of the gastrointestinal tract, plus its contents, and in the feces; no detectable radioactivity was found in any other tissue, body fluid, or expired CO_2. From these results, the authors concluded that nitrocellulose was not absorbed by the rat.

Nitrocellulose was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 when tested at concentrations as high as 5000 g/plate with or without S-9 metabolic activation (Ellis et al., 1978).

DERIVATION OF PROVISIONAL ORAL RfD VALUES FOR NITROCELLULOSE

Although the intestinal absorption study (Ellis et al., 1976) was limited, by analogy to cellulose, nitrocellulose is unlikely to be absorbed from the gut in mammals, except ruminants. The portal-of-entry effects observed in rats and mice are likely the result of either the compaction of nitrocellulose (or cellulose in general) in the intestinal tract causing a physical blockage or a reduction of the nutritive content of feed. These effects are considered not relevant to humans because of the larger diameter of the human intestinal tract and the implausibility of consumption of such high levels of nitrocellulose by humans. In addition, nitrocellulose will not likely be taken up by plants or animals, nor is it soluble in water, so there is little potential for exposure to humans in food or water from contaminated sites. As a result, the p-RfD for nitrocellulose can be set to the highest exposure level tested in mammalian species that did not

result in physical impairment of nutrition. This level is 8485 mg/kg-day in the 13-week dietary study in dogs (Ellis et al., 1976). The p-RfD for both subchronic and chronic exposure is derived as follows:

Subchronic and Chronic p-RfD = NOAEL ÷ UF
= 8485 mg/kg-day ÷ 3
= **3000 (3×10^3) mg/kg-day**

The chronic dog study (Ellis et al., 1980), with a lower NOAEL than the subchronic study, is not used as the basis for the chronic p-RfD because it is not plausible that continued exposure will lower the effect level (there being none). The composite uncertainty factor (UF) of 3 accounts for potentially sensitive humans who might experience gastrointestinal distress at high exposures. Specifically, the factor of 3 is for the dynamic component of UF_H. As exposure will be limited physically and there is virtually no likelihood of systemic effects in humans, all other uncertainty factors are set to 1. Systemic toxicokinetic and toxicodynamic differences within humans and across species are not relevant. In addition, there does not seem to be a need for additional interspecies uncertainty because the data suggest that the only limiting factors across species are the size of the intestinal lumen (leading to blockage in smaller animals) and dietary insufficiency, both of which will not be factors for humans. The lack of developmental toxicity studies, too, is not a concern because of the lack of systemic distribution of nitrocellulose.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR NITROCELLULOSE

No information is available on the subchronic or chronic inhalation toxicity of nitrocellulose, which precludes derivation of RfC values for this chemical.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR NITROCELLULOSE

Weight-of-Evidence Descriptor

Information on the carcinogenicity of nitrocellulose in humans is available from an epidemiological study of a plastics plant that produced nitrocellulose (cellulose nitrate) and a variety of other chemicals, including cellulose acetate, styrene polymers, polyvinyl chloride, polyvinyl butyral, and phenolic and melamine resins (Marsh, 1983). Mortality among workers was investigated using a matched case-control study nested within a retrospective cohort design. Analysis of job and work location variables suggested a possible association between rectal cancer and cellulose nitrate production. The odds ratios for all digestive system cancers combined showed an increase with length of exposure to cellulose nitrate production, although not at statistically significant levels ($p > 0.05$). For specific digestive system cancers, a statistically significant odds ratio of 8.90 was found based on four cases for rectal cancer among workers employed in cellulose nitrate production for periods greater than 5 years. These

findings are only *suggestive* of a possible association between cellulose nitrate production and rectal cancer due to the concurrent multiple chemical exposures, small number of deaths, and other study limitations.

Information on the carcinogenicity of nitrocellulose in animals is available from the 24-month oral studies in rats, mice, and dogs (Ellis et al., 1980). Comprehensive histopathological evaluations showed no increases in neoplastic lesions in any of the species at dietary concentrations as high as 3% (1280−1422, 4866−6056, and 1013−1034 mg/kg-day in rats, mice and dogs, respectively) and 10% (4076−4576 mg/kg-day in dogs, doses not available in rats and mice due to excessive feed scattering).

Nitrocellulose was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 when tested with or without S-9 metabolic activation (Ellis et al., 1978). In vivo testing in rats showed 10% nitrocellulose in the diet did not induce chromosomal aberrations in peripheral blood lymphocytes or kidney cells after 13 weeks of exposure (Ellis et al., 1976) or bone marrow or kidney cells after 24 months of exposure (Ellis et al., 1980). Excessive scattering of feed precludes an accurate estimation of dose.

As summarized above, the chronic oral studies of nitrocellulose in animals demonstrate a lack of carcinogenic effect in three species (rats, mice, and dogs) (Ellis et al., 1980). These findings are consistent with the expectation that the treated animals, like humans, cannot digest cellulose and passed the fibers through the digestive tract unabsorbed. This nondigestion of nitrocellulose was confirmed in an oral absorption study (Ellis et al., 1976). After repeated gavage doses (once daily for 4 days) of ^{14}C-nitrocellulose to rats, radioactivity was recovered only in various parts of the gastrointestinal tract plus its contents and in the feces; no detectable radioactivity was found in any other tissue, body fluid or expired CO_2. Additionally, there is no indication that nitrocellulose is genotoxic (Ellis et al., 1976, 1978, 1980). In accordance with current U.S. EPA cancer guidelines (U.S. EPA, 2005), the available data inadequate for an assessment of human carcinogenic potential of nitrocellulose following oral exposure.

For inhalation exposure, the occupational epidemiology study (Marsh, 1983) is only *suggestive* of a possible association between nitrocellulose production and rectal cancer in humans. There is no additional information regarding the carcinogenicity of nitrocellulose by the inhalation route of exposure. In accordance with current EPA cancer guidelines (U.S. EPA, 2005), the available data are inadequate for an assessment of human carcinogenic potential of nitrocellulose following inhalation exposure.

Quantitative Estimates of Carcinogenic Risk

Due to the lack of data in support of carcinogenicity, it is neither possible nor appropriate to derive quantitative estimates of carcinogenic risk for nitrocellulose for either oral (p-OSF) or inhalation (p-IUR) exposures.

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