a significant economic impact on a substantial number of small entities.

Executive Order 12372

The program/activity is listed in the Catalog of Federal Domestic Assistance under No. 10.025 and is subject to Executive Order 12372, which requires intergovernmental consultation with state and local officials. (See 7 CFR Part 3015, Subpart V.)

List of Subjects in 9 CFR Part 92

Animal diseases, Canada, Imports, Livestock, and livestock products, Mexico, Poultry and poultry products, Quarantine, Transportation, Wildlife.

PART 92—IMPORTATION OF CERTAIN ANIMALS AND POULTRY AND CERTAIN ANIMAL AND POULTRY PRODUCTS; INSPECTION AND OTHER REQUIREMENTS FOR CERTAIN MEANS OF CONVEYANCE AND SHIPPING CONTAINERS THEREON

Accordingly, we are adopting as a final rule, without change, the interim rule amending 9 CFR 92.2(i)(1) that was published at 54 FR 12897–12898 on March 29, 1989.

Authority: 7 U.S.C. 1622, 19 U.S.C. 1306; 21 U.S.C. 102–105, 111, 134a, 134b, 134c, 134d, 134f, and 135; 31 U.S.C. 9701; 7 CFR 2.17 2.51, and 371.2(d).

Done in Washington, DC, this 23rd day of June 1989.

James W. Glosser,

Administrator, Animal and Plant Health Inspection Service.

[FR Doc. 89–15399 Filed 6–28–89; 8:45 am]

BILLING CODE 3410–34–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 510

Animal Drugs, Feeds, and Related Products; Change of Sponsor Name

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect a change of sponsor name from Nutrius, Inc., to Bioproducts, Inc.

EFFECTIVE DATE: June 29, 1989.

FOR FURTHER INFORMATION CONTACT: Benjamin A. Puyot, Center for Veterinary Medicine (HFV–130), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 301–443–1414.

SUPPLEMENTARY INFORMATION: Bioproducts, Inc., Two Brecksville Commons, 8221 Brecksville Rd., Brecksville, OH 44141, advised FDA of a change of corporate name from Nutrius, Inc., to Bioproducts, Inc. The agency is amending the regulations in 21 CFR 510.600(c) (1) and (2) to reflect the change.

List of Subjects in 21 CFR Part 510

Administrative practice and procedure, Animal drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs and redelegated to the Center for Veterinary Medicine, Part 510 is amended as follows:

PART 510—NEW ANIMAL DRUGS

1. The authority citation for 21 CFR Part 510 continues to read as follows:

Authority: Secs. 512, 701(a) (21 U.S.C. 360b, 371(a)); 21 CFR 5.10 and 5.83.

2. Section 510.600 is amended in the table in paragraph (c)(1) by removing the entry "Nutrius, Inc., and by alphabetically adding a new entry "Bioproducts, Inc., and in paragraph (c)(2) in the entry "051359" by revising the sponsor name to read as follows:

§ 510.600 Names, addresses, and drug labeler codes of sponsors of approved applications.

(c)
(1)*

Firm name and address	Drug labeler code
Bioproducts, Inc., Two Brecksville Commons, 8221 Brecksville Rd., Brecksville, OH 44141	051359

(2)*

Drug labeler code	Firm name and address
051359	Bioproducts, Inc., Two Brecksville Commons, 8221 Brecksville Rd., Brecksville, OH 44141.

Dated: June 23, 1989.

Robert C. Livingston,

Deputy Director, Office of New Animal Drug Evaluation, Center for Veterinary Medicine.

[FR Doc. 89–15354 Filed 6–28–89; 8:45 am]

BILLING CODE 4160–01–M

21 CFR Part 700

[Docket No. 85N–0536]

RIN 0905–AC00

Cosmetics; Ban on the Use of Methylene Chloride as an Ingredient of Cosmetic Products

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations to ban the use of methylene chloride as an ingredient of cosmetic products. Scientific studies have shown that inhalation of methylene chloride causes cancer in laboratory animals. The available information shows that the continued use of methylene chloride in cosmetic products may pose a significant risk to human health, especially to specific segments of the population that are continually exposed to aerosol cosmetics containing this ingredient. Therefore, the agency has decided to take this action because it has concluded that cosmetic products that contain methylene chloride may be injurious to users under their conditions of use.

EFFECTIVE DATE: August 28, 1989, for products initially introduced or initially delivered for introduction into interstate commerce.

FOR FURTHER INFORMATION CONTACT: Terry C. Troxell, Center for Food Safety and Applied Nutrition (HFF–312), Food and Drug Administration, 200 C St. SW Washington, DC 20204, 202–485–0229.

SUPPLEMENTARY INFORMATION:

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I. Background

A. Description of Methylene Chloride

Methylene chloride (CAS Reg. No. 75–09–2, dichloromethane) is a colorless, volatile liquid that is used in a variety of consumer and industrial products as a solvent and flame suppressant. The primary cosmetic use of methylene chloride has been in hair sprays. Because of its volatility, it causes quick drying and setting of the applied hair spray resin.

Methylene chloride has also been used in foods as an extraction solvent in the processing of coffee beans, spices, and hops. When used in this manner, methylene chloride is a food additive within the meaning of section 201(s) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(s)). Methylene chloride has also been used in the manufacture of food-contact articles. In some of these cases, methylene chloride may be a food additive within the meaning of section 201(s) of the act, while in other cases, methylene chloride may remain as an impurity in the indirect food additive. The food uses of methylene chloride are beyond the scope of this final rule on cosmetic uses.

B. Procedural History

In the **Federal Register** of December 18, 1985 (50 FR 51551), FDA proposed to prohibit the use of methylene chloride as an ingredient of cosmetic products. The agency stated that the data before it revealed that methylene chloride is carcinogenic by inhalation to the liver and lung of male and female mice. It also stated that the data suggested that this substance has a tumorigenic effect on the mammary glands of female rats and produces sarcomas of the salivary gland/integument of rats upon inhalation (50 FR 51551). Therefore, the agency tentatively concluded that methylene chloride is an animal carcinogen by inhalation and may be carcinogenic to humans.

Epidemiology studies and other information that FDA considered at the time of the proposal did not alter the agency's tentative conclusion. The proposal described the agency's assessment of the risk to humans from exposure to methylene chloride used in hair spray-type cosmetics. FDA estimated the upper bound lifetime risk of cancer from the lifetime use of hair sprays containing methylene chloride to be in the range 10^{-3} (1 in 1,000) to 10^{-4} (1 in 10,000) for the consumer and in the range 10^{-2} (1 in 100) to 10^{-3} (1 in 1,000) for the hair care specialist. Therefore, the agency proposed to find that the use of this substance as an ingredient in cosmetics may render those cosmetics injurious to the health of users.

In the proposal, the agency deferred consideration of the food uses of methylene chloride listed in the food and color additive regulations, except for its use in decaffeinating coffee beans, because the agency knew of no indications of a hazard to the public health from these uses. With regard to its use in decaffeinating coffee, the agency stated that even though methylene chloride had been shown to be carcinogenic by inhalation, no action on this use was necessary because any risk from the low exposures resulting from this use would be essentially nonexistent.

On February 24, 1986 (51 FR 6494), the agency extended the comment period on the proposal until April 4, 1986, to provide additional time for comments on the use of methylene chloride as a decaffeinating agent. On October 10, 1986, FDA received four new studies concerning comparative pharmacokinetics, metabolism, and genotoxicity of methylene chloride. These studies were sponsored by the European Council of Chemical Manufacturers' Federation (CEFIC). The agency reopened the comment period for 30 days on December 5, 1986 (51 FR 43935), to allow an opportunity for comment on these new studies. After the close of this comment period, the agency received several additional submissions relevant to the methylene chloride proceeding, including reports of studies extending the pharmacokinetic and metabolism work, two reports on pharmacokinetic (PB–PK) modeling, and an epidemiology study on Canadian General Electric employees. Although FDA has not formally reopened the comment period for this new information, the information has been on display at the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm 4–62, 5200 Fishers Lane, Rockville, MD 20857 in the file on this rulemaking for several months and has been considered by the agency.

C. Description of Comments

About 60 comments were submitted during the comment periods from consumers, consumer groups, industry associations, and manufacturers. Three comments were sent in during the reopened comment period on the CEFIC studies. Some comments included data and reports of studies concerning methylene chloride. Reports of genotoxicity studies, pharmacokinetics and metabolism of methylene chloride in different mammalian species, pharmacokinetic modeling, and new and expanded epidemiology studies were submitted. Information on human exposure to methylene chloride was also submitted.

Twelve of the comments agreed with FDA's proposal to prohibit the use of methylene chloride in cosmetics. Five comments expressed disagreement with the proposed ban and argued for continued use in cosmetics. The majority of the comments that stated a position on the use of methylene chloride in the decaffeination of coffee and wanted the use ended. Many of the comments expressed an opinion only and did not provide supporting data or arguments. The substantive comments relevant to the cosmetic use and FDA's response to each are discussed below.

II. Methylene Chloride—Decaffeination of Coffee

In the proposal, the agency stated that it was not proposing to change the existing regulation (21 CFR 173.255) authorizing the use of methylene chloride for decaffeination of coffee. The agency stated that even though methylene chloride had been shown to cause cancer, the residue limitation for this substance prescribed in § 173.255(c) provided safe conditions of use for this additive. The agency based its position on two factors. First, on evaluating the risk from use of the additive for decaffeinating coffee under the intended conditions of use, the agency determined that the potential carcinogenic risk is negligible. Second, FDA determined that the Delaney anticancer clause of the Food Additives Amendment (section 409(c)(3)(A) of the act (21 U.S.C. 348(c)(3)(A))) does not require a ban in this case because the risk is negligible, and that there would be no significant gain to the public health if this use of methylene chloride were banned.

This determination was based on the principle that the law does not concern itself with trifling or de minimis matters. The agency also applied this principle in listing the color additives D&C Red No. 19 and D&C Orange No. 17 which the agency found to be carcinogenic but to present insignificant risk under their prescribed conditions of use. The agency's decision to list these color additives was reviewed by the U.S. Court of Appeals for the District of

Columbia as a result of a suit filed by the Public Citizen Litigation Group (*Public Citizen* v. *Young*, 831 F.2d 1108 (D.C. Cir. 1987)). In its opinion, dated October 23, 1987 the court held that "* * the Delaney Clause of the Color Additive Amendments does not contain an implicit de minimis exception for carcinogenic dyes with trivial risks to humans, and that the listing of carcinogenic color additives is contrary to law. The court, however, made no decision about the food additive Delaney clause, stating in the discussion on food additives:

> Moreover, we deal here only with the color additive Delaney clause, not the one for food additives. Although the clauses have almost identical wording, the context is clearly different.

On April 18, 1988, the U.S. Supreme Court denied a petition for a writ of certiorari that had been filed by the Cosmetic, Toiletry and Fragrance Association.

The agency expects that it will take a substantial amount of time for it to consider what effect, if any, the court decision in *Public Citizen* v. *Young* will have on FDA's regulation of food additives, including methylene chloride. Therefore, to avoid further delay in acting on the proposed ban of the use of methylene chloride in cosmetics, the agency has decided to separate the cosmetic and food additive issues and to defer any necessary action on the food additive use of methylene chloride until a future date. FDA will consider the substantive comments that it has received in this rulemaking that pertain to the food additive use of methylene chloride in developing any action on this issue.

III. Introduction—Safety Assessment

In 1985, the Office of Science and Technology Policy (OSTP), in describing how to assess the human cancer risk associated with chemical exposure, captured the essential features of any safety assessment that FDA conducts:

> The first [step], which is often referred to as hazard identification, entails a qualitative evaluation of both the data bearing on an agent's ability to produce carcinogenic effects and the relevance of this information to humans. The second, exposure assessment, is concerned with the number of individuals who are likely to be exposed and with the types, magnitudes, and durations of their anticipated exposures. The third component, hazard or dose-response assessment, uses the information on carcinogenicity from the hazard identification phase together with mathematical modeling techniques to estimate the magnitude or an upper bound on the magnitude of the carcinogenic effect at any given dose level. Finally, one may combine the information from the first three components or steps to characterize the carcinogenic risk associated with the expected human exposure to the compound of interest.

[50 FR 10436 and 10437· March 14, 1985]

The OSTP discussion also provides a convenient structure for this document. FDA will first consider the comments that it has received that bear on the agency's evaluation of the carcinogenic hazard posed by methylene chloride to humans. Second, it will evaluate the comments that bear on the agency's assessment of the extent of exposure to methylene chloride from its use in cosmetics. Third, it will evaluate the comments on the magnitude of the hazard that those who are exposed face. Finally, the agency will consider comments on its tentative determination that the hazard is sufficiently large that use of methylene chloride in cosmetic products will render those products adulterated.

However, before beginning this evaluation, the agency will consider a number of comments that it received that asserted that FDA consideration of the safety of the use of methylene chloride in cosmetics was premature.

(1) Five comments received during the comment period which closed April 4, 1986, stated that the agency should wait for new information from the pharmacokinetic, metabolism, and epidemiology studies that were in progress before reaching any conclusion on methylene chloride. A trade association said it was cooperating with the National Cancer Institute (NCI) to develop a new epidemiology study. It pointed out that relevant information would be presented at meetings and workshops during 1986. Another trade association stated that it was sponsoring comparative metabolic studies on methylene chloride.

Adequate time has elapsed for submission of studies that were in progress when the proposal issued on December 18, 1985. The agency has received and considered in this rulemaking final reports on epidemiology, metabolism, pharmacokinetics, cytotoxicity, and genotoxicity studies that were in progress at the time of the proposal and, in some cases, that were initiated after the proposal was issued.

The new epidemiology study that was to be done in cooperation with NCI has not been undertaken to date. At a June 10, 1987 meeting, NCI's advisory panel on the proposed epidemiology study recommended against proceeding with the study because the methylene chloride exposure levels were too low and the potential size of the cohort too small to achieve the desired goals (Ref. 1). While NCI apparently has not totally abandoned the possibility of further epidemiology work, FDA does not believe that it is appropriate to delay action further for a study that has not been started and may not be done.

(2) Several comments said that the agency had not adequately reviewed the available metabolism, pharmacokinetics, and human epidemiology data on methylene chloride.

FDA did review the available studies on these subjects before publishing the proposal but made only very brief comments on them because the data from these studies were insufficient to affect its decision. The pharmacokinetic and metabolism data available before the proposal was published did not provide convincing evidence to the agency on the mechanism of carcinogenesis of methylene chloride. Therefore, the agency was not able to use this information in risk assessment. Furthermore, the agency could not draw any definitive conclusions from the available epidemiology studies because of study design limitations, such as the small number of workers and the short period of exposure. Additional data on these and other subjects that are related to the toxicity of methylene chloride were submitted to the agency in response to the proposal. FDA has carefully reviewed all of the available information on the metabolism, pharmacokinetics, genotoxicity, cytotoxicity, and human epidemiology of methylene chloride in reaching the decision announced in this final rule. The agency's evaluations of these complex issues are discussed in the following sections on the individual subjects.

IV Hazard Identification—The Carcinogenicity of Methylene Chloride

A. Introduction

The proposal described several recent chronic studies on methylene chloride, some of which raise questions about the safety of the chemical: (1) the National Toxicology Program (NTP) sponsored inhalation studies in rats and mice; (2) the National Coffee Association (NCA) sponsored drinking water studies in rats and mice; and (3) the three inhalation studies, two in rats and one in hamsters, performed by The Dow Chemical Co. (Dow).

In the proposal, FDA stated its tentative conclusions on the carcinogenicity studies. From the NTP mouse study, the agency concluded that "* * methylene chloride is carcinogenic to the liver and lung of

male and female mice. This study also demonstrates that methylene chloride induces cancer at a site (the liver) remote from the tissue directly exposed by the inhalation treatment" (50 FR 51551).

The agency also concluded that the results in the NTP rat inhalation study are suggestive of a tumorigenic effect of methylene chloride on the mammary glands of the female rats. FDA concluded that the observations from this NTP rat study and from the high dose rat study conducted by Dow provide suggestive evidence that methylene chloride also induces sarcomas of the salivary gland/integument in rats upon inhalation.

There were no treatment-related neoplastic effects observed in the Dow inhalation study with hamsters or in the NCA drinking water studies with rats and mice.

B. Comments on FDA's Evaluation of the Available Carcinogenicity Studies

(3) In discussing the methylene chloride carcinogenicity studies, one comment said that several experimental studies other than the NTP bioassay have also reported increases in mammary and liver tumors. The comment did not identify any such studies, however.

None of the carcinogenicity studies for which FDA has reports, other than the NTP study on mice, showed significant increases in liver tumors. The NTP and Dow inhalation studies indicated slight increases in the incidence of benign mammary tumors in rats. The agency cannot say conclusively that these increases were treatment-related effects but considers them to be suggestive evidence.

The comment may be referring to studies mentioned in a talk presented by Prof. C. Maltoni, Bologna, Italy, at a 1984 workshop on methylene chloride (Ref. 2). Prof. Maltoni stated in his talk that he had found an increased incidence of mammary tumors and liver nodular hyperplasia in his methylene chloride study with rats. However, despite numerous requests by the organizers of the workshop for a manuscript of his talk to distribute to participants, including FDA toxicologists, no written reports have been received. Consequently, the agency cannot use these studies in its decision.

(4) One comment contended that there is not sufficient evidence to call methylene chloride a carcinogen because positive results from a single study in a single species do not provide sufficient evidence to call a substance a carcinogen except where unusual tumors are found that do not occur spontaneously, or where the tumor incidence can be related to an alkylating agent.

FDA believes that the comment provides an incorrect description of the evidence on methylene chloride. As explained in the proposal, the agency has considered and carefully evaluated seven chronic studies of methylene chloride.

In the NTP 2-year inhalation study in mice, methylene chloride induced significantly increased incidences in alveolar/bronchiolar adenomas, alveolar/bronchiolar carcinomas, and alveolar/bronchiolar adenomas and carcinomas (combined) in male and female mice of both dose groups compared to the controls. Methylene chloride also induced significantly increased incidences of hepatocellular adenomas in high-dose male and female mice, of hepatocellular carcinomas in high-dose males and low- and high-dose females, and of the combined adenomas and carcinomas in all treated groups of both sexes. These increased incidences were distinctly dose related.

In addition, other biological evidence from this study is consistent with the carcinogenic effect of methylene chloride in mice. There were dose-related increases in the incidences of mice bearing multiple tumors of either the lung or liver. None of the control mice with lung tumors had more than one lung tumor, whereas more than 37 percent of lung tumor-bearing mice in both treated groups and in both sexes had multiple lung tumors. Only 9 percent of control males and none of control females had multiple tumors in the liver. In contrast, 46 percent of low-dose males, 48 percent of high-dose males, 19 percent of low-dose females, and 70 percent of high-dose females had multiple liver tumors. The percentage of mice having both lung tumors and liver tumors also increased in a dose-related fashion (Ref. 3).

There is also supporting evidence from studies conducted with rats. There was an increase in incidence of salivary gland sarcomas in the Dow inhalation study with rats that appears to be related to treatment. Two of these same tumors that are rarely observed spontaneously occurred in the high dose treatment groups of the NTP rat study. The agency also found evidence suggestive of a tumorigenic effect of methylene chloride on the mammary glands of female rats in both the NTP and the Dow studies.

Therefore, the agency concludes that there is sufficient evidence that methylene chloride has a carcinogenic effect in $B_6C_3F_1$ mice of both sexes, and that there is supporting evidence in another species, the rat. IARC reached a similar conclusion in its recent evaluation. It concluded that, "There is sufficient evidence for the carcinogenicity of dichloromethane to experimental animals" (Ref. 4). Finally, NTP concluded, with respect to their inhalation study on methylene chloride, that there was clear evidence of carcinogenicity in $B_6C_3F_1$ mice and female F344 rats and some evidence of carcinogenicity in male F344 rats (Ref. 5).

(5) Four comments argued that the mammary gland tumors in the rats exposed to methylene chloride in the NTP study are not evidence of true carcinogenicity. They said that these were benign tumors, and that the tumors did not progress to malignant tumors. Furthermore, the comments characterized the incidences of the mammary tumors at the lower dose levels as within the range of historical controls and the top dose response as barely above the highest incidences in historical controls. The comments noted that IARC considers increases of only malignant tumors as sufficient evidence of carcinogenicity, and that the Past Presidents of the Society of Toxicology have said that when incidence rates in treated groups are within historical control ranges, differences between treated and concurrent control groups are not biologically significant.

The agency has not used the mammary tumorigenic effect in rats as the primary evidence for the carcinogenicity of methylene chloride. Rather, the agency has stated that the evidence of lung and liver tumors in mice provides an appropriate basis to conclude that methylene chloride is carcinogenic in mice of both sexes.

As stated in response to comment 4, however, the agency believes that data from the rat studies provide supporting evidence of the carcinogenicity of methylene chloride. FDA also points out that, as mentioned in the comments, the incidence of mammary tumors in at least the high dose group was above, rather than within, the range of historical controls. The evidence of a dose-response effect in the induction of mammary fibroadenomas in the female F344 rats in the NTP study is suggestive of a tumorigenic effect of methylene chloride. Observations from Dow's studies lend further support to an indication of a tumorigenic effect of this chemical in rat mammary glands.

(6) Four comments urged caution in determining carcinogenicity from the increased incidences of the types of tumors that occur spontaneously at high incidences in untreated groups. The

comments argued that the lung and liver tumors found in mice exposed to methylene chloride in the NTP study are types of tumors that occur spontaneously with high and variable incidence. The comments cited statements made by several expert bodies in support of their argument and quoted IARC as saying: [T]here are certain neoplasms, including lung tumors and hepatomas in mice, which have been considered of lesser sigificance than neoplasms occurring at other sites for the purpose of evaluating the carcinogenic risk of chemicals to humans. The comments also pointed out that similar statements have been made in documents issued by OSTP and by the Environmental Protection Agency (EPA).

The agency agrees with this concern and is fully aware of the difficulties encountered in the interpretation of a tumor response at a site of high background incidence. Although the male $B_6C_3F_1$ mice have relatively high spontaneous tumor incidences in the liver and lung, the female mice generally have low background rates at these organ sites (Ref. 6). Thus, these comments bear consideration only for the males. Yet, in the NTP inhalation studies, methylene chloride was shown to induce significant increases above the background rate in incidences of lung and liver tumors in both sexes of mice.

These increases were distinctly dose related. In addition, other biological evidence strongly supports the carcinogenicity of methylene chloride in both sexes of mice. This evidence includes the increased incidences of dosed mice bearing multiple lung or liver tumors as compared to control mice, and the increased incidences of dosed mice having both lung and liver tumors in the same animal.

FDA is aware that the relevance of hepatocellular tumors in mice for predicting cancer risk in humans has been debated extensively over the past several years. This debate does not obviate the need for a careful evaluation of each study in which there is a finding of an elevated incidence of hepatocellular tumors and a determination as to whether the finding is valid.

Finally, even though IARC holds the general position cited in the comments, IARC itself concluded in the specific case of methylene chloride that there is sufficient evidence for its carcinogenicity in animals (Ref. 4).

(7) Two comments took issue with a point in the proposal that they understood to be a statement that the salivary gland sarcomas in treated rats in the NTP study provide suggestive evidence of carcinogenicity. One comment argued that these sarcomas lack significance. This comment argued that the agency's apparent position was unwarranted because the NTP draft transcript indicated that there was no evidence of salivary gland anomalies related to treatment, and because one such tumor was found in a control rat in the earlier Dow study. The other comment stated that these sarcomas are not discussed in the draft NTP report.

In the proposal, FDA considered the significance of the Dow and NTP results together. The agency pointed out that there was an increased incidence of male rats with sarcomas in the region of the salivary gland in the high-dose Dow inhalation study, and that there were two sarcomas of the salivary gland/integument in treated rats in the NTP study. The fact that these rare tumors were seen in the NTP study adds some credibility to the results of the Dow study even though by themselves the occurrence of these two tumors would arouse little suspicion. Therefore, FDA does not find any significance in the fact that NTP did not discuss these tumors.

FDA pathologists have had the opportunity to review the morphologic characteristics of the salivary gland sarcomas seen in Dow's inhalation study in Sprague-Dawley rats (Ref. 7) and of the two salivary gland sarcomas in the NTP study with F344 rats. The morphologic pattern of the latter tumors is unusual but similar to that of the salivary gland sarcomas found in the Dow study. The agency considers the presence of two unusual salivary gland tumors in the NTP study and the occurrence of a larger number of salivary gland sarcomas in the Dow study to be suggestive evidence of a treatment related effect.

(8) One comment stated a belief that the agency used data for calculating potency different from those data given in the draft NTP report for the female mice treated by inhalation of 2,000 parts per million (ppm) methylene chloride. The comment stated that this belief was based on a calculation using the cancer potency of 4.4×10^{-4} (mg/kg/day)$^{-1}$ (i.e., 4.4×10^{-4} per milligram per kilogram of body weight per day) stated by the agency in the proposal.

The agency did use the dose and tumor incidence data that were presented in the draft NTP report in calculating the carcinogenic potency of methylene chloride. However, the agency described the calculations only in general terms in the proposal. The following discussion provides further details.

FDA computed the carcinogenic potency as the risk (the probability that an animal will develop a tumor) divided by the dose that produced that risk (Ref. 8). To estimate the risk, the agency considered the lung and liver neoplasia of the 2,000 ppm-treated female mice to be independent and added them together. Therefore, the sum of the tumor incidences in this group of mice becomes approximately 100 percent (33 percent for liver neoplasms plus 63 percent for the lung neoplasms, as reported in the NTP report). To calculate the dose, the ageney converted dose expressed in air concentration (ppm) to a body weight (bw) basis. For methylene chloride, 1 ppm = 0.0035 milligram per liter (mg/L). Thus, 2,000 ppm = 7 mg/L. The mice were dosed 6 hours per day for 5 days out of 7 Using an inhalation rate of 0.025 liter per minute (L/minute) for the mouse, the time weighted average dose is 7 mg/L × 0.025 L/minute × 60 minutes/hour × 6 hours/day × 5 out of 7 days = 45 mg/day. For a 20-gram-mouse, the dose thus becomes 45 mg/day/0.020 kg = 2250 mg/kg bw/day. Therefore, the carcinogenic potency = 1/2250 = 4.4×10^{-4} (mg/kg bw/day)$^{-}$

C. Cytotoxicity Data and Evaluation

(9) Some comments declared that the lung tumors in the mouse could be explained by the cytotoxicity of methylene chloride to the nonciliated bronchiolar epithelial (Clara) cells in the lungs. They said that the Clara cell had been shown to be the cell of origin of lung tumors for several chemicals. They suggested that the sensitivity of the Clara cells to methylene chloride seen in the mouse was not likely to occur in humans. The comments submitted evidence to support the point that there is Clara cell injury in mice, but not in rats, when exposed to methylene chloride and argued that this finding correlated with the occurrence of lung tumors in mice but not in rats.

The comments also submitted evidence that they believed demonstrated that the cytotoxicity of methylene chloride resulted in the loss of the ability of Clara cells to metabolize methylene chloride by one (the mixed function oxidase (MFO) pathway, also referred to as the cytochrome P-450 pathway) of the two known metabolic pathways (a sequence of enzyme-catalyzed reactions by which a cell metabolizes a compound) for methylene chloride. They argued that the loss of this pathway would result in greater metabolism by the second metabolic pathway (the glutathione-S-transferase (GST) pathway) and "have a significant impact on the risk of those cells becoming malignant" because, these comments believe, the GST metabolism

is responsible for the lung and liver tumors. One comment pointed out that the number, distribution, and ultrastructural morphology of Clara cells in mouse lungs are different from those in humans and other animals.

In support of these comments, reports entitled "Methylene Chloride (Dichloromethane): 10-Day Inhalation Toxicity Study to Investigate the Effeets on Rat and Mouse Liver and Lungs and "Methylene Chloride (Dichloromethane): The Effects of Exposure to 4000 ppm on Mouse Lung Enzymes, conducted by Imperial Chemical Industries, were submitted (Refs. 9 and 10).

The agency has evaluated both of these studies. While the results of these studies on the cytotoxicity of methylene chloride may be relevant to the observed lung cancer induction in mice, the agency finds that at best they provide, as stated by the investigators, only circumstantial evidence that the Clara cell is the cell of origin of the lung tumors in the case of methylene chloride. The reported cytotoxicity to the Clara cells was observed in 10-day studies. Cytotoxicity studies of this duration are not adequate to explain the mechanism by which mice get lung tumors after 2 years of treatment.

Scientific debate persists on the cells of origin of chemically-induced lung tumors in mice. Some investigators believe that the lung tumors in mice are derived solely from alveolar type II cells. Some assume that they arise from Clara cells. Others believe that lung tumors in mice may arise from either alveolar type II or Clara cells (Refs. 11 and 12). NTP in the report on the bioassay of methylene chloride, did not identify the cell of origin of the mouse lung tumors. It classified the tumors only as alveolar/bronchiolar adenomas or carcinomas (Ref. 5).

Consequently, the agency concludes that the evidence submitted with the comment does not support the claim that the lung tumors arise from cytotoxic effects on the Clara cells, or that the Clara cells are necessarily the cell of origin of the lung tumors. The relationship, if any, among the cytotoxic effects in the Clara cells observed during subacute exposure to methylene chloride; the lung cancer, a chronic effect found in the NTP study on mice; and potential carcinogenesis in humans, is not clear.

D. Genotoxicity Studies and Findings

(10) Three comments argued that methylene chloride is not carcinogenic for humans. In support of this argument, the comments asserted that methylene chloride is not genotoxic because it does not act directly on mammalian deoxyribonucleic acid (DNA). They pointed out that the available experiments did not show alkylation of DNA, or unscheduled DNA synthesis (UDS), by methylene chloride in rats or mice. One comment discussed a number of mutagenicity studies and concluded that, although there were some positive genotoxic responses to methylene chloride in some bacteria, yeasts, and plants, the effects in these simpler systems do not necessarily bear on animal cells. The comments asserted that the genotoxicity testing that has been done in animal cells, including a micronucleus test, yielded doubtful or negative results.

The comments argued that this information should be used in evaluating the mechanism of cancer induction because it suggests that methylene chloride causes only a secondary effect on DNA, and that this secondary effect should have a threshold below which no carcinogenic effect would be expected.

A consumer organization argued that the micronucleus test for genetic damage sheds little light on the potential for methylene chloride to be hazardous to humans.

The agency has evaluated the relevant studies on the genotoxicity of methylene chloride, including new studies that were submitted with the comments. The agency does not agree that methylene chloride has been shown to be nongenotoxic. After evaluating all the available data (Ref. 13), including the above mentioned studies, the agency concludes that the evidence on the genotoxicity of methylene chloride is inconclusive.

Methylene chloride was positive in several types of tests (Ref. 13). The agency finds that methylene chloride induces mutation in *Salmonella typhimurium, Escherichia coli*, and mouse lymphoma cells; gene conversion and mitotic recombination in *Saccharomyces cerevisiae*; chromosomal aberrations in Chinese hamster ovary cells; DNA damage in *E. coli*; and transformation in SA7 adenovirus-infected Syrian hamster embryo cells, mouse BALB/3T3 cells, and Fischer 344 rat cells infected with C-type virus. The results on induction of sister chromatid exchange were positive in one study and negative in another study, although the reasons for this discrepancy are not clear. The agency places greater weight on the positive result because the effect was reproduced in different tests performed within the study.

Methylene chloride was negative in other tests (Ref. 13). It did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* micronuclei in mouse bone marrow; or UDS in rat hepatocytes, primary human fibroblasts, and hamster V79 cells. The results of the in vivo DNA binding study with rat and mouse liver and lung also were negative under the experimental conditions employed.

The agency believes that the results in some studies that were reported to be negative are questionable (Ref. 13). The negative results of the in vitro and in vivo/in vitro studies for UDS with mouse hepatocytes are questionable because of the lack of cytotoxicity information on mouse hepatocytes exposed to methylene chloride in vitro or in vivo and because of the slight but significant increases in the percentage of cells in repair which suggests that a higher concentration might induce a positive response. The results of the tests for chromosomal aberrations in rat bone marrow are also questionable because, in addition to the more commonly observed chromatid and chromosomal breaks, an exchange figure and rings, which are significant chromosomal aberrations, were observed at the two highest doses tested. Finally, although no actual data were included in the report on a micronucleus test in *Tradescantia paludosa*, the summary table in the report indicates that the response was borderline.

The agency does not agree that the genotoxic effects observed in the assays on methylene chloride are not relevant to animal cells. A simple demarcation between different kinds of cells cannot be made. Although there were both positive and negative results with methylene chloride, positive responses were obtained with various types of cells, including animal cells, and these findings indicate that this chemical is potentially genotoxic to animal cells. Data obtained in the cell transformation assays together with that from the genetic assays appear to signal the potential oncogenicity of methylene chloride.

The agency also cannot agree with the hypothesis that methylene chloride acts through a secondary mechanism rather than a direct effect on DNA. Although the genetic toxicology assay results are not conclusive, given these results, the agency cannot exclude the possibility that methylene chloride has a direct genotoxic effect on animal DNA.

Therefore, the agency concludes that the genotoxicity studies do not provide a basis on which to conclude that methylene chloride is not carcinogenic for humans.

V. Exposure Assessment

(11) One comment agreed broadly with FDA's findings on human exposure levels from the use of methylene chloride in cosmetics and submitted a review of available information on exposure from consumer and professional use of hair spray containing methylene chloride to assist the agency in this rulemaking. The review included studies involving fluorocarbons and dimethyl ether and two reports on methylene chloride that the agency had not evaluated earlier.

FDA has evaluated the information submitted concerning exposure to methylene chloride from aerosol cosmetics. The new data do not differ substantially from the data that FDA previously used. The agency concludes that its tentative findings are appropriate (Ref. 14).

(12) One comment discussed the calculation of 8-hour time-weighted average exposure estimates for humans through hair spray use. The comment stated that FDA prorated the mouse inhalation exposure to a 24-hour time-weighted average without similarly prorating the human exposure to the same basis and said that this procedure is incorrect.

The comment is incorrect. In calculating the risks discussed in the proposal, the agency used two different dose-scaling methods for comparing the exposure of the mice in the NTP inhalation study to the probable exposure of humans (Ref. 8). These methods employ 24-hour time-weighted average concentrations of methylene chloride, one expressed in parts per million in air and one in milligrams of methylene chloride per kilogram body weight per day. In each case, the agency used the same 24-hour time-weighted basis for humans as for mice. The risks that were discussed in the proposal do not change if an 8-hour time-weighted average exposure is used for both species rather than a 24-hour time-weighted average exposure.

VI. Dose Response Assessment

A. Introduction

In the proposal, the agency estimated the risk from the use of methylene chloride in cosmetics by extrapolating from the incidence of benign and malignant neoplasms in female mice exposed to 2,000 ppm methylene chloride in the NTP study to average human exposure from use of the aerosol cosmetics. For the extrapolation, the agency assumed a linear dose-response model. By this procedure, FDA estimated the upper bound lifetime risk of cancer from the use of hair sprays containing methylene chloride to be in the range 10^{-3} (1 in 1,000) to 10^{-4} (1 in 10,000) for the consumer and in the range 10^{-2} (1 in 100) to 10^{-3} (1 in 1,000) for the hair care specialist.

B. How to Estimate Risk

(13) Some comments stated that FDA should use the principles outlined in the OSTP document "Chemical Carcinogens: A Review of the Science and Its Associated Principles, February 1985" as guidelines for doing risk assessment (50 FR 10372; March 14, 1985).

The agency has adopted the principles for doing risk assessment of chemicals that are set out in the OSTP review and has applied them in the risk assessment for methylene chloride. For example, the agency has used low dose linearity in its risk extrapolation for methylene chloride as recommended in the OSTP document for cases, like methylene chloride, where there is uncertainty about the mechanism of carcinogenicity.

(14) Two comments stated that the agency should incorporate all available data into its risk evaluation process and should make a best estimate of true risk for methylene chloride, not just a worst-case analysis.

The agency incorporates all the available data into its risk assessment process to the extent that it is appropriate to do so based on considerations such as validation of studies and uncertainties in the data. The agency uses upper bound estimates of risk to account for the uncertainties in the data and in the risk assessment procedures. Because of these uncertainties, attempts to develop "best" estimates of true risk may underestimate true risk in specific instances. Therefore, to avoid underestimating risk, the agency relies upon upper bound estimates in making regulatory decisions that involve the public health.

(15) Two comments said that the agency's quantitative risk estimates are highly exaggerated because of many conservative assumptions. They suggested that the agency use a more realistic risk assessment model. They contended that the risks from the use of methylene chloride in hair spray are not significant. One of these comments referred to a similar comment it had sent to FDA earlier complaining that FDA's Sensitivity of the Method (SOM) Carcinogen Policy [50 FR 45530; October 31, 1985] also exaggerated risk estimation in the context of carcinogenesis in certain animal drugs.

The agency agrees that the risk estimates from exposure to methylene chloride discussed in the proposal may be exaggerated. In fact, the agency characterized its risk estimates as being an upper bound. To assure public health protection, however, FDA believes that risk assessment procedures should include upper bound estimates. FDA, in its risk assessment for methylene chloride, used conservative assumptions where data relating to any particular element of the assessment were either absent or inconclusive. On the other hand, FDA agrees that the best available information should be used to avoid unnecessarily conservative estimates.

As discussed elsewhere in this document, the agency has now incorporated into its risk assessment every valid piece of information available to it. Having used this information, the agency finds that the estimated upper bound risks from the use of aerosol cosmetics that contain methylene chloride are high enough that it is appropriate to conclude that the use of these cosmetics may be injurious to the health of consumers and of hair care professionals.

The SOM rulemaking resulted in the promulgation of regulations to deal with cancer-causing residues in edible products of food-producing animals as the result of administration of drugs, food additives, or color additives and, therefore, is not directly relevant to this rulemaking on methylene chloride in cosmetics. Although the principles underlying the SOM approach are similar to those used here to estimate the risk, the estimation of risk under the SOM approach is more complex because of the need to assess two exposures, exposure of the animal to the drug or additive and exposure of the human to the carcinogenic residue remaining in the animal. All issues relating to exaggeration in the SOM risk estimation were addressed in that rulemaking.

(16) A few comments said that the agency should not use a nonthreshold model for risk extrapolation for methylene chloride but should consider that the situation may have a threshold. They claimed that methylene chloride is not a genotoxic carcinogen.

The selection of the appropriate model for estimating cancer risks at low doses is often extremely difficult because of the lack of information on the mechanism of carcinogenesis and on the dose response for the chemical. In most cases, the models require many theoretical assumptions about the mathematical form of the dose-response relationship and the mechanisms underlying the cancer induction.

A great deal of uncertainty still remains about the mechanism of action