

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. 1822, 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
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Bioproducts, Inc., Two Brecksville Commons, 8221 Brecksville Rd., Brecksville, OH 44141	051359
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(2)*

Drug labeler code	Firm name and address
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051359	Bioproducts, Inc., Two Brecksville Commons, 8221 Brecksville Rd., Brecksville, OH 44141.
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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 B₆C₃F₁ 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 B₆C₃F₁ 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 significance 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 B₆C₃F₁ 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 agency 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 $7 \text{ mg/L} \times 0.025 \text{ L/minute} \times 60 \text{ minutes/hour} \times 6 \text{ hours/day} \times 5 \text{ out of } 7 \text{ days} = 45 \text{ mg/day}$. For a 20-gram-mouse, the dose thus becomes $45 \text{ mg/day} / 0.020 \text{ kg} = 2250 \text{ mg/kg bw/day}$. Therefore, the carcinogenic potency = $1 / 2250 = 4.4 \times 10^{-4}$ (mg/kg bw/day)⁻¹.

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 Effects 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

of methylene chloride. Questions about the genotoxicity of methylene chloride, and about how metabolism of this substance affects its carcinogenicity, have not been convincingly resolved. Therefore, the agency does not believe that the available evidence is sufficient to show that a threshold exists for tumor induction by methylene chloride or to show how to determine that threshold, if one does exist. In the absence of convincing evidence for a threshold or of knowledge of the mechanism of carcinogenesis, as an agency charged with protection of the public health, FDA will continue to rely on a nonthreshold procedure to estimate risk for exposures below the measured dose response.

C. Metabolic and Pharmacokinetic Data

1. Comments

(17) FDA received three comments in response to the proposal that, based on how methylene chloride is metabolized in certain animals, advocated the use of a physiologically-based pharmacokinetic (PB-PK) model approach for estimating the risk from methylene chloride. In May 1986, the agency received a preprint of a paper by Andersen et al. on the PB-PK model and risk assessment for methylene chloride (Ref. 15). (The agency had received preliminary drafts of this paper from Dr. Richard Reitz of Dow before publication of the December 1985 proposal.) In October 1986, CEFIC submitted papers on in vivo inhalation pharmacokinetics and metabolism of methylene chloride in rats and mice (Ref. 18) and on in vitro metabolism of methylene chloride in rat, mouse, and hamster liver and lung fractions and in human liver fractions (Ref. 19).

On December 5, 1986, FDA reopened the comment period for public comment on these studies, as well as on two studies concerning the genotoxicity of methylene chloride that were also submitted by CEFIC in October 1986 (51 FR 43935).

FDA received three comments during the reopened comment period. Two comments simply stated that the studies were of excellent quality and should be accepted by the agency. The third comment was from a consumer organization. It stated that the four CEFIC studies do not support CEFIC's contention that methylene chloride is not carcinogenic to humans. The comment pointed out that no correlations between a metabolic pathway and lung cancer in humans can be made because human lung tissue has not been tested. The comment questioned the relevance of in vitro

studies to in vivo conditions because species may differ in various ways that affect the reactions in intact organisms. In addition, the comment noted that the metabolic studies do not explain the bioassay evidence for carcinogenicity in rats. It also emphasized that different species may differ in the organ site affected and in sensitivity to a carcinogen.

After the close of the December 1986 comment period several more reports were submitted by CEFIC and Dr. Reitz. In July 1987 Dr. Reitz submitted a report on in vitro studies on GST metabolism of methylene chloride in preparations from mouse, rat, and hamster lung and liver tissues and human liver tissues and on the implications of the results of these studies for PB-PK based risk estimation (Ref. 20). In November 1987 CEFIC submitted three additional reports on methylene chloride: (1) A report on in vivo inhalation pharmacokinetics in mice and rats (Ref. 21), (2) a report on in vitro GST metabolism in rat, mouse, hamster, and human liver cytosol fractions (Ref. 22), and (3) a report on the effects of exposure to 4,000 ppm methylene chloride on mouse lung enzymes (Ref. 10). In early 1988, Dr. Reitz submitted a preprint of a scientific paper on in vitro metabolism studies of methylene chloride, incorporation of these data into the PB-PK model for methylene chloride, and risk estimation (Ref. 16). In June 1988, CEFIC submitted a report on human risk assessment of methylene chloride based on PB-PK modeling that incorporated CEFIC's recent pharmacokinetic and metabolism results and on two risk extrapolation procedures (Ref. 17).

2. The Metabolic Hypothesis

The comments from CEFIC, Dr. Reitz, and colleagues argued that the evidence submitted in response to the proposal, as well as the considerable body of research existing before the proposal, support the following hypothesis:

Methylene chloride is metabolized via two metabolic pathways in mammals (Ref. 23). These pathways (according to this hypothesis) account for virtually all of the metabolism of methylene chloride. One pathway is the mixed function oxidase (MFO) pathway, also referred to as the cytochrome P450 pathway. This oxidative pathway is located in the smooth endoplasmic reticulum of cells and is present in the human, rat, hamster, and mouse. It saturates (i.e., higher dose levels of methylene chloride do not significantly increase the amount of this substance that is metabolized by this pathway) at about 500 ppm inhalation exposure in rats and mice.

The second pathway is referred to as the GST pathway. This pathway is located in the soluble fraction of the cytoplasm and produces carbon dioxide as the end product (Ref. 24). This pathway does not saturate at high doses and is more active in its metabolism of methylene chloride in the mouse than in humans or in other mammals.

The comments hypothesized that reactive intermediates produced during the metabolism of methylene chloride by the GST pathway cause changes that lead ultimately to the formation of tumors found in the NTP bioassay on the mouse. The comments postulated further that neither methylene chloride itself nor the intermediates or products of the MFO pathway contribute to this carcinogenic effect.

The theory presented in these comments uses a PB-PK model for assessing and comparing the internal exposure of tissues to toxic chemicals and their metabolites in mammalian species. The PB-PK model mathematically simulates the absorption, distribution, metabolism, and elimination of methylene chloride in different species. These comments argued that with the use of the proper anatomical, physiological, and metabolic parameters, the PB-PK model approach allows the use of the "internal dose" to the target organ in the quantitative assessment of risk. The comments argued that use of this internal dose is more appropriate than use of the external dose of the parent compound and permits more realistic high dose to low dose and interspecies extrapolations in the quantitative assessment of risk.

The comments stated that the metabolic data and PB-PK modeling correlate well with the bioassay data and thus support the hypothesis that the GST pathway produces the carcinogenic metabolite. They pointed to the relatively high levels of GST metabolites in mouse lung and liver, where tumors were produced, as compared to the levels calculated with the PB-PK model for the respective organs in the rat and hamster, in which no increased incidences of liver or lung tumors were observed.

The comments also argued that, in contrast, the metabolic data for the MFO pathway do not correlate well with the bioassay findings for the lung and liver. The comments pointed out that the metabolism studies by Green et al., Reitz et al., and others have shown that MFO metabolism approaches saturation at exposure levels lower than those used in the inhalation bioassay on the mouse. Once saturation is reached,

concentration of MFO metabolic products would not increase with increasing dose levels of methylene chloride. If an MFO metabolite were responsible for the cancer, the comments argued, then cancer incidence also should not increase at dose levels above the saturation dose. Yet, there is a dose-related increase in cancer incidence with methylene chloride at doses above MFO pathway saturation in the mouse study. In addition, the hamster bioassay was negative even though the MFO metabolic rates in the liver preparations were comparable to the rates in the mouse preparations. For these reasons, the comments concluded that the MFO pathway does not produce a carcinogenic metabolite during metabolism of methylene chloride.

In support of their claim that the parent, unmetabolized methylene chloride is not responsible for the cancer induction in the NTP inhalation bioassay, the comments contended that methylene chloride has a very low level of chemical reactivity. They argued that therefore it is unlikely that this substance can directly react with DNA, and that, if it could, methylene chloride would be expected to be an extremely weak alkylating agent.

The comments stated that the pharmacokinetic data of Green et al. (Ref. 18) show higher blood, and presumably lung and liver, concentrations of methylene chloride in rats than in mice inhaling 2,000 ppm or 4,000 ppm of methylene chloride. They stated that the induction by methylene chloride of liver and lung tumors only in mice and not in rats supports their postulate that unmetabolized methylene chloride is not responsible for inducing tumors.

The comments included data on in vitro metabolism of preparations made from a limited number of human liver and 2 human lung autopsy samples. The comments stated that the evidence shows that the activity of the GST pathway is at least 10 times lower in human liver and lung than in the respective tissues in the mouse. Furthermore, because of the relatively weak affinity of methylene chloride to the GST enzyme, the MFO pathway would metabolize a greater proportion of the methylene chloride than the GST pathway at the very low exposures typically encountered by humans as compared to the high dose levels used in the mouse bioassay, where the MFO pathway became saturated. Based on the hypothesized carcinogenic metabolic pathway, the metabolism data, PB-PK modeling, and several quantitative risk extrapolation procedures, the comments

concluded that the "internal dose" of GST metabolites in lung and liver is small for humans exposed to methylene chloride from hair sprays, and that the carcinogenic risk to the lung and the liver presented by this use is insignificant.

The crucial postulates for the mechanism of methylene chloride carcinogenicity proposed by the comments are: (1) The metabolism of methylene chloride in mice, rats, hamsters, and humans by two and only two significant pathways, (2) the lack of direct carcinogenic activity of methylene chloride itself at all doses, (3) the lack of carcinogenic activity of MFO metabolites at all doses and the saturation of this pathway at higher doses, and (4) the carcinogenicity of GST metabolites and their increased importance at higher doses as the metabolism of methylene chloride is increasingly shifted to the GST pathway. The evidence bearing on these propositions is discussed below. In brief, the agency believes that the evidence appears to support postulates (1) and (3), but it has significant reservations about the validity of postulates (2) and (4).

3. FDA's Response

The agency did not use either metabolic data or pharmacokinetic models in the risk assessment that it published in the proposal of December 18, 1985, although it did consider them. At the time of publication of the proposal, the agency did not believe that the available pharmacokinetic information on methylene chloride was sufficiently complete for it to accept the hypothesized mechanism and the model based on this mechanism, or for it to adjust the estimated risk for either the lung or liver tumors on the basis of this mechanism.

In developing this final rule, the agency has evaluated all studies relevant to the pharmacokinetics and metabolism of methylene chloride, particularly the new information submitted in response to the proposal, and considered their impact on the risk assessment that FDA has done for this chemical (Ref. 25).

Based on the available evidence, the agency agrees that the MFO and GST pathways appear to be the principal metabolic routes of elimination of methylene chloride.

The agency also agrees that the submitted in vivo and in vitro metabolic data support the postulated saturation of the MFO pathway at high doses. The agency believes that the observed correlation between the PB-PK model predictions of MFO metabolite levels in

the target organs and the bioassay results in rodents is consistent with the postulated lack of carcinogenic activity for the MFO metabolites.

Moreover, the agency believes that the results of the pharmacokinetics and metabolism studies, as well as of the PB-PK modeling, show a correlation between GST metabolism data and certain bioassay results. In vitro GST metabolic activity is high in the mouse liver, where methylene chloride caused cancer in the NTP bioassay, and in vitro GST activity is lower or not detected in rat and hamster lung and liver, where no increase in incidence of cancer was observed.

However, there is an apparent contradiction of the hypothesis from the data reported for GST metabolism in mouse lung tissue. The contradiction is that in vitro GST metabolic activity in lung tissue is only a small fraction of the activity in mouse liver tissue. Nevertheless, lung tumors were induced at approximately the same level as liver tumors. Moreover, in rat liver tissue the in vitro GST metabolic activity was greater than in mouse lung tissue. However, liver tumors were not induced in the rat.

To explain this apparent contradiction, CEFIC hypothesized that the Clara cell is the cell of origin of pulmonary tumors, and that most of the metabolism takes place in these cells. CEFIC postulated that, because Clara cells make up only about 5 percent of lung tissue, and presumably the amount of GST metabolism is proportionately higher in these cells than in the other cells of the lung, the Clara cells may be exposed to considerably higher levels of GST metabolites than other pulmonary cells. CEFIC argued that this could explain the contradiction because the Clara cells would be exposed to comparable levels of GST metabolites as mouse liver tissue.

As discussed in comment 9, the cell of origin of the lung cancer in the mouse was not identified by NTP or anyone else. Furthermore, the comment's postulate on the cellular origin of the lung tumors is based in part on the assumption that the GST metabolic activity of Clara cells is high as compared to the GST metabolic activity of other types of lung cells in the mouse. No data on relative GST pathway metabolic activity with methylene chloride in different lung cells were presented to support this assertion. The agency concludes that the submitted evidence does not demonstrate that the Clara cell is the cell of origin of the lung tumors in the mouse, or that GST pathway metabolism of methylene

chloride is elevated in these cells. Thus, the contradiction described above remains unexplained.

A further problem in accepting the hypothesis that methylene chloride induces cancer in animals through the production of GST metabolites is that proponents have not provided a clear and self-consistent picture of this mechanism. On the one hand, they argued that the GST pathway produces a genotoxic intermediate that was responsible for the cancer observed in the NTP study with mice (Ref. 26). On the other hand, they argued that methylene chloride produces its effects by a nongenotoxic mechanism and asserted that a threshold model would be most appropriate for risk extrapolation of the PB-PK calculated "internal" dose of the GST metabolites presumably because these metabolites are nongenotoxic (Refs. 15 and 26). Such inconsistencies with respect to the mechanism make it more difficult for the agency to credit the hypothesis.

Another problem relates to the role of the parent, unmetabolized methylene chloride in carcinogenesis. The arguments presented in the comments that parent, unmetabolized methylene chloride plays no direct role in the induction of cancer by inhalation have some merit. However, in the mouse bioassay, the cells lining the lung in particular are continuously exposed to high concentrations of the parent, unmetabolized methylene chloride upon inhalation. The comments have not demonstrated that the parent methylene chloride plays no role in the carcinogenicity, especially in the lung. That methylene chloride has not been found to interact with DNA in rodent liver and lung may be the result of inadequate sensitivity of current methods. It is known that methylene chloride is mutagenic in some tests with microorganisms where there is no metabolic activation through added microsomal preparations. Also, it is possible that the parent methylene chloride may induce tumors by a mechanism that does not involve DNA alkylation.

The evidence cited by the comments does not differentiate between the case for unmetabolized methylene chloride and the case for some metabolite from the GST pathway being responsible for tumor induction. The exposure of the lung to both unmetabolized methylene chloride and metabolites from the GST pathway increases with increasing external dose of methylene chloride as does the incidence of lung tumors. The evidence only appears to rule out any substantial role for metabolites from the

MFO pathway. (This pathway is saturated at high doses, and the amount of MFO metabolites do not increase with increasing dose. Thus, this saturation is inconsistent with the observed tumor incidence in the mouse which does increase with increasing dose.)

Moreover, not only is it possible that unmetabolized methylene chloride is solely responsible for inducing the lung tumors in the mouse, but more than one chemical species, methylene chloride and one or more of its metabolic derivatives, could be responsible. If unmetabolized methylene chloride is involved in the induction of lung tumors, either alone or in combination with metabolites, the PB-PK model predicts that there will be no significant alteration of risk by using "internal" dose from that presented in the proposal using external dose.

Furthermore, the agency believes that the lack of lung and liver tumors in the rats, which were exposed to high levels of methylene chloride, could have resulted from factors other than difference in metabolism, such as a difference in intrinsic sensitivity between mouse and rat.

In addition, as discussed in the proposal and comments 4, 5, and 7 there is suggestive evidence of a tumorigenic effect of methylene chloride on mammary glands and salivary glands in rats for which no mechanistic or pharmacokinetic information is available.

The comments have not met their burden of demonstrating that the adjustments in the risk assessment that they have suggested are appropriate. Therefore, the agency concludes that the estimated risk to humans should not be changed from the estimates in the proposal based on the pharmacokinetic and metabolic data and hypothesized GST metabolic mechanism of carcinogenicity.

D. Epidemiology in Risk Assessment

1. The Kodak Study

(18) Seven comments contended that the agency should use the data from human epidemiology studies in the evaluation of methylene chloride. Some of these comments said that the new information in an expanded study on Kodak employees exposed to methylene chloride is now adequate to be used, instead of animal testing data, to analyze the risks from methylene chloride use. They also stated that the epidemiology data do not indicate a risk of cancer for humans from use of methylene chloride.

On the other hand, one comment stated that epidemiological studies on methylene chloride are inadequate to determine carcinogenicity in humans because of design limitations, such as small sample size, ill-defined exposure levels, and insufficient latency periods.

A cohort of employees chronically exposed to methylene chloride at the Eastman Kodak facility in Rochester, NY, has been followed since 1964, and its mortality experience has been examined (Refs. 27, 28, and 29). The agency has reviewed the reports on this epidemiology study as completely as possible (Refs. 30, 31, and 32).

The agency finds that the most recent update on the Eastman Kodak study on the chronic health effects of methylene chloride contains improvements over the original report on this study (Ref. 27) and the 1980 update (Ref. 28), including a larger sample of workers, improved exposure estimates, and an effective average latency period. The agency also finds, however, that because the average levels at which the Kodak employees were exposed to methylene chloride were very low, the study has only a limited ability to detect an increase in cancer risk.

Hearne et al. in the most recent update of this study (Ref. 29), draw two major conclusions from their analysis: (1) That the epidemiology data show no adverse health effects associated with exposure to methylene chloride through 1984, and (2) that predictions of risk of neoplasia to humans based upon extrapolation from methylene chloride animal studies are "clearly inconsistent" with human experience. FDA agrees that the study did not detect an increased risk of cancer among employees exposed to methylene chloride. However, FDA's analysis of the available data shows that the upper bound potency (unit risk) implied by the human epidemiology study is consistent with the risk estimated from animal data (Ref. 31).

To compare the results of the epidemiology study with the animal bioassay evidence on the carcinogenicity of methylene chloride, the Kodak investigators used the cancer incidence of the NTP mouse study to calculate the excess number of methylene chloride-exposed workers (that is, the number above the background rate) predicted to die through 1984 from lung or liver cancer. The upper bound on the excess lung and liver cancer deaths that might occur in humans through 1984 that the investigators calculated based on the animal data was larger than the number of such deaths actually found by the

epidemiology study. For this reason, the Kodak investigators concluded that the animal data are inappropriate for estimating the risk of methylene chloride to humans.

However, in extrapolating from the animal data to estimate this upper bound on the excess worker deaths expected, the Kodak investigators used a number of assumptions and adjustment factors that FDA does not believe are valid (Ref. 31). Using what FDA believes to be more realistic interspecies comparative assumptions and lifetime adjustment factors, the agency calculated that far fewer excess lung and liver cancer deaths would be expected through 1984 among the methylene chloride-exposed workers than were predicted by the Kodak investigators (Ref. 31).

The Kodak investigators concluded only that the potential upper bound human risk of methylene chloride, calculated using linear-at-low-dose extrapolation from the animal data, is clearly inconsistent with the epidemiology results. This conclusion is hardly surprising, however, since it is of course unlikely that the actual risk of dying from lung or liver cancer is as high as the conservatively estimated upper bound risk. The actual risk can be anywhere from zero to the upper bound estimate.

FDA has found that the Kodak epidemiology study is marginally adequate to detect excess deaths from lung and liver cancer if the risk of these cancers for the exposed workers is 160 percent that of the unexposed workers, but that the study is not able to reliably detect lower risks (Ref. 31). FDA calculations show that the highest risk predicted by the animal data would be no more than 140 percent that of unexposed workers at the exposure levels experienced by the Kodak cohort (Ref. 31), a level of risk that is thus not detectable by the Kodak epidemiology study.

Therefore, FDA does not believe that the data from the Eastman Kodak human epidemiology study refute the animal evidence of the carcinogenicity of methylene chloride or the upper bound human risk calculated from the most sensitive species tested (mouse).

2. The General Electric Study

(19) The agency received two documents, including a preprint of a paper submitted for publication in a scientific journal (Ref. 33), that describe an epidemiology study on women employees in the coiling and wire drawing area of the lamp manufacturing department at the Canadian General Electric plant in Toronto, ON, Canada.

The study investigators reported a higher than normal occurrence of breast and gynecological cancers among these employees. The submitters of this study believe that the study implicates methylene chloride as the causative agent.

The agency disagrees that this study shows an association between methylene chloride and the reported excess breast and gynecological cancers found in women employees (Ref. 34). No exposure assessment was done, either qualitatively or quantitatively, for methylene chloride. Although methylene chloride is on a list of chemicals purchased for use in the coiling and wire drawing area in 1984, there is no indication as to how much was actually used in 1984 or other years; as to the methylene chloride levels present in the coiling and wire drawing area; and as to the methylene chloride levels present in other areas of the plant. Finally, the study investigators themselves state that no conclusions can be drawn about the relationship between the use of methylene chloride and the reported increase in cancer.

In addition, the agency believes that the finding of a significant excess of breast and gynecological cancers in this study is of questionable validity. This result was obtained by grouping increases in breast cancer and gynecological cancer incidence that were individually insignificant, without increasing the criterion for statistical significance to allow for a greater number of comparisons. In fact, if the appropriate adjustment for multiple comparisons is made, the study does not show a significant increase in the incidence of breast and gynecological cancer among these employees.

VII. Characterizing the Risks

(20) One comment suggested that there is only weak evidence that methylene chloride is a carcinogen. The comment pointed out that the International Working Party of Experts had developed a set of categories for classifying carcinogens. The comment argued that methylene chloride should be placed in the fourth of these categories, which includes substances that have only potential relevance to humans and that do not require an automatic regulatory response.

The agency does not agree with the comment's conclusion on evidence of carcinogenicity. As explained above, the agency has determined that the evidence of carcinogenicity for methylene chloride is sufficient to conclude that this substance is an animal carcinogen. An International Agency for Research on Cancer (IARC)

working group also reviewed the carcinogenicity data on methylene chloride and concluded that "There is sufficient evidence for the carcinogenicity of dichloromethane to experimental animals" (Ref. 4.). Furthermore, 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).

(21) Some comments objected to the agency's proposal on the basis that it called methylene chloride a probable human carcinogen.

In the proposal of December 18, 1985, FDA did not state that methylene chloride was a probable human carcinogen, but rather that methylene chloride "may be carcinogenic to humans. FDA based this statement on the findings from animal bioassays. It is the agency's policy that substances that are carcinogenic to animals, as methylene chloride has been found to be, should be considered potential human carcinogens unless there is evidence to the contrary.

Rodent species such as rats and mice have been accepted by the scientific community as appropriate surrogates for humans in toxicity testing, including carcinogenesis testing. Experimental evidence has established a high correlation between the ability of a substance to induce cancer in rodents and its ability to induce cancer in humans (Refs. 35, 36, and 37). The agency concluded, based on the NTP inhalation studies on rodents and other relevant information, that methylene chloride is an animal carcinogen by inhalation. Because methylene chloride induces cancer in rodents, it may also do so in humans. This view is shared by IARC, which stated that "in the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence for carcinogenicity in animals as if they presented a carcinogenic risk to humans" (Ref. 38). To ensure protection of the public health, the agency will treat positive results from well-conducted carcinogenicity studies in animals as strong evidence that the compound considered represents a carcinogenic hazard to humans and will characterize the risk using these studies unless evidence from studies on humans indicates otherwise.

(22) One comment stated: According to the FDA, 1 in every 100 hairdressers will die from continued use of aerosol hair sprays that contain methylene

chloride. This is clearly an unacceptable risk.

The agency did not state that a number of hairdressers will die from this use. The proposal said that for hair care specialists, the upper bound of lifetime risk of contracting cancer (not the risk of dying) is in the range of 1 in 100 to 1 in 1,000. This estimate is not an actuarial risk. Moreover, it does not refer to every hairdresser but only to those that use aerosol cosmetic products that contain methylene chloride consistently over a prolonged period. Nonetheless, the agency does believe, based on the available data, that there is a significant potential risk to users. Therefore, the agency is prohibiting the use of methylene chloride in aerosol cosmetics.

VIII. Other Comments

A. Halogenated Solvents Industry Petition

(23) The Halogenated Solvents Industry Alliance (HSIA) submitted a petition (Docket No. 86P-0443) requesting that FDA terminate its rulemaking to ban the use of methylene chloride as an ingredient in cosmetic products. HSIA argued that there are apparently acceptable substitutes for methylene chloride in cosmetics, and that, to their knowledge, "all or virtually all manufacturers or formulators have now switched to other ingredients for cosmetic uses in which methylene chloride was previously employed. Thus, HSIA concluded that actual consumer exposure is truly de minimis, and that no benefits would result from regulating the use of methylene chloride in cosmetics. HSIA stated further that, because consumer exposure to methylene chloride from cosmetics is negligible, it is unnecessary and inappropriate for FDA to continue devoting resources to resolving scientific uncertainties inherent in what would now be only a hypothetical situation. HSIA cited as its basis regulatory policy guideline number 4 from the August 11, 1983, Report of the Presidential Task Force on Regulatory Relief, "Reagan Administration Regulatory Achievements, which is referenced in section 1(d) of Executive Order 12498. Guideline number 4 states that regulations should address risks that are real and significant rather than hypothetical or remote. HSIA further requested that FDA reopen the comment period for submission of comments on the issue of actual use and consumer exposure if FDA believes that additional data are needed to show the absence of any use of methylene chloride in cosmetics.

The agency does not agree that a regulation prohibiting use of methylene chloride as an ingredient in cosmetics is no longer necessary. The agency is concerned that in the absence of a regulation prohibiting such use, firms could subject the public to methylene chloride exposure from aerosol cosmetic products at any time. Until recently, the information available to the agency was consistent with HSIA's claim that methylene chloride is not being used as an ingredient in cosmetic products. However, the agency received a letter dated November 30, 1988, from a law firm stating that its client uses methylene chloride in certain aerosol cosmetic products. This letter explained that this company had removed methylene chloride from its products after FDA published its proposal, but that the company decided to resume use of methylene chloride because company officials believed that (1) more favorable information had appeared to support the safety of methylene chloride, (2) FDA had stayed the final action (which it had not), and (3) consumers of their products preferred them formulated with methylene chloride.

The company's actions demonstrate why this regulation is needed to avoid ambiguity about both the legal status of methylene chloride and the risk associated with its use. Although the agency could take enforcement action under section 601 of the act (21 U.S.C. 361) in cases involving the use of methylene chloride in a cosmetic product when the agency becomes aware of such a product, the agency believes that a prohibitive regulation is a more effective way of protecting the public health. This regulation provides notice to future as well as current manufacturers of cosmetic products that methylene chloride should not be used because of the significant potential risk.

With respect to application of regulatory policy guideline number 4, the agency has concluded that methylene chloride may be a human carcinogen, and that the potential risk from the use of this substance in cosmetics is not hypothetical or remote. Furthermore, a primary concern of guideline 4 is cost-benefit assessment. If, as HSIA argued, manufacturers were no longer using methylene chloride in cosmetics, and if, as HSIA presumably believed, a prohibitive regulation is not necessary to preclude the use of methylene chloride in cosmetics, this action would have no or negligible costs. The resumption of use of methylene chloride by one manufacturer that has methylene chloride-free formulations available

does not change the conclusion that the costs of this action will be negligible.

B. Other Agencies Regulation of Methylene Chloride

(24) Two comments pointed out that the Environmental Protection Agency (EPA), the Consumer Product Safety Commission (CPSC), and the Occupational Safety and Health Administration (OSHA), as well as FDA, are evaluating the data on methylene chloride. The comments argued that these other agencies are not proposing any regulatory action at this time and urged FDA not to be precipitous in acting on methylene chloride. These comments urged FDA to be consistent with the other agencies.

FDA is aware of the consideration of methylene chloride by other agencies. However, each agency administers different statutes, and its regulatory response must meet the requirements of the applicable statute.

FDA's findings are consistent with the conclusions of the CPSC on methylene chloride. On August 20, 1986 (51 FR 29778), CPSC proposed to find that methylene chloride may be a human carcinogen by inhalation and may be considered a hazardous substance under the Federal Hazardous Substances Act (FHSA). Without withdrawing the proposed rule, CPSC published a notice of interpretation and enforcement policy on September 14, 1987 (52 FR 34698). This notice concluded that "the Commission believes that household products that present a significant exposure to methylene chloride vapor are hazardous substances due to a potential hazard of human carcinogenicity. CPSC stated its intention to bring enforcement actions under FHSA for products that do not comply with the labeling required by FHSA for hazardous substances. Full compliance of labels for these products was required by September 14, 1988.

FDA also notes that OSHA published an advance notice of proposed rulemaking on methylene chloride (51 FR 42257 November 24, 1986) in which it concluded that there is sufficient evidence of carcinogenicity in two species and positive indications of mutations in three organisms, but that the human epidemiology data are inconclusive. In addition, EPA has initiated a regulatory investigation [50 FR 42037 October 17 1985].

Concerning the timing of FDA's action relative to actions by other agencies, FDA believes that, when faced with a public health hazard such as the hazard from methylene chloride in aerosol cosmetics, it is obligated to act when it

has a sound basis for a decision. FDA has completed its evaluation of the comments and other relevant information and has determined that it has a sound basis for this action. Therefore, FDA is taking this action even though other agencies may not have reached the same point in their rulemaking.

C. Effective Date

(25) Three comments requested that any final regulation to prohibit the use of methylene chloride in cosmetics provide more time than that provided in the proposal for distribution of products already manufactured and for development of replacement products. One comment requested a 6-month period and a second comment requested at least a 1-year period between publication of the final order and its effective date to allow reformulation of products and testing for stability.

The agency proposed that a regulation in this proceeding would take effect 60 days after the date of publication of the final rule and would be applicable only to products initially introduced or initially delivered for introduction into interstate commerce after that time. This final rule affirms the 60-day period between publication and the effective date. Thus, the ban applies only to products initially introduced or initially delivered for introduction into interstate commerce on or after August 28, 1989. Products introduced into interstate commerce before that date will not be affected.

FDA concludes that a 6-month or a 1-year delay in the effectiveness of this regulation is not necessary. The 60-day period following the publication of this final rule is sufficient for cosmetic manufacturers to comply with the requirements of this regulation.

Information submitted by a trade association and a law firm and the results of a survey of firms participating in the voluntary filing of cosmetic product ingredient statements (under 21 CFR Part 720) demonstrate that the manufacturers of hair sprays generally reformulated their products to replace methylene chloride either before or shortly after the publication on December 18, 1985, of the proposal to ban its use as a cosmetic ingredient. Furthermore, firms have had more than 3 years' notice of this action and, therefore, have had ample time to refine methylene chloride-free formulations and to develop contingency plans to deal with the proposed 60-day effective date. Accordingly, the agency believes that the 60-day period is sufficient for the manufacturers and the marketers of aerosol cosmetics to resolve whatever

matters may be pending with respect to the manufacture and distribution of their methylene chloride-free formulations.

D. Request to Reopen Record

(26) One comment in a letter dated November 30, 1988, requested that FDA reopen the record to reconsider the need to ban the use of methylene chloride in aerosol cosmetics based on new risk assessment data submitted to FDA in June 1988. The comment also stated that, if FDA still chooses to ban methylene chloride, the agency should inform consumers in the preamble to any final rule as to the lack of any proof that methylene chloride presents a risk to humans when used in aerosol cosmetic products.

The agency disagrees that the record should be reopened. Even though the report submitted in June 1988 (Ref. 18) was submitted to the agency well after the close of the last official comment period (January 5, 1987), the agency reviewed it, as well as other reports that were submitted late, and found nothing in these reports that would affect FDA's decision to prohibit the use of methylene chloride as an ingredient in cosmetics. Furthermore, the new information has been on display at the Dockets Management Branch in the file on this rulemaking for a number of months. Therefore, the agency believes interested persons have had ample opportunity to comment on it.

FDA also disagrees that it should inform consumers that there is no proof that methylene chloride presents a risk to humans when used in aerosol cosmetic products. It is because of the evidence that risks to consumers may be high that the agency is concluding that methylene chloride as an ingredient in cosmetics may render these cosmetics injurious to users. If FDA were convinced that there was no evidence that this use of methylene chloride presented a significant public health hazard, the agency would not issue this rule prohibiting this use of methylene chloride.

IX. Summary and Conclusions

After evaluating all available data the agency concludes that methylene chloride is carcinogenic by inhalation in mice, and that there is suggestive evidence of a tumorigenic effect of methylene chloride in rats.

Epidemiological data on workers exposed to methylene chloride do not indicate any carcinogenic effect in humans. However, FDA finds that the sensitivity of the study is insufficient to rule out the possibility that methylene chloride can cause cancer in humans, as inferred from the rodent studies.

Substantial new information on the metabolism and mechanism of action of methylene chloride was submitted to the agency. Several comments argued that these metabolic data should be incorporated into the carcinogenic risk assessment process through the use of a physiologically-based pharmacokinetic model approach.

The postulated metabolic mechanism is that the carcinogenicity of methylene chloride in rodents, and any potential carcinogenicity in humans, is caused solely by the formation of active GST metabolites. FDA concludes that this postulated mechanism is scientifically plausible but has not been adequately supported. The available evidence is insufficient to explain how lung or liver tumors were caused in the mouse by the postulated mechanism and to rule out that inhaled methylene chloride directly causes lung tumors in mice, and that it may have the same effect in humans. Therefore, the agency has not used the physiologically-based pharmacokinetic model approach to reduce the estimated risk of cancer for users of aerosol cosmetics containing methylene chloride. Consequently, the agency affirms that the estimated risks presented in the proposal are appropriate upper bound estimates of risk for humans exposed to methylene chloride from aerosol cosmetics.

Because the exposure to methylene chloride from hair spray use can be high, the potential cancer risk from this use may be high. Therefore, the agency concludes that methylene chloride is a poisonous or deleterious substance that may render cosmetic products injurious to users.

X. Impact Analyses

In the proposed rule, the agency explained that the effects of this action had been considered in accordance with the Regulatory Flexibility Act and with Executive Order 12291.

(27) One comment said that the proposal violated Executive Orders 12498 and 12291 because the agency did not make the best estimates of the risks from methylene chloride uses, only extremely conservative estimates. The comment argued that without the best estimates of risks, it is not possible to know what value to put on the costs of the action or what degree of protection the public received from the action.

The agency disagrees with the comment and finds that it is possible to estimate the cost of the proposed ban without a best estimate of risk. The agency estimated the cost of the proposed ban in its threshold assessment in 1985 by calculating the

amount of methylene chloride then used in cosmetics, the changes required by a ban, and the costs of these changes. The agency found that the proposed action did not meet the criteria for a major rule described in Executive Order 12291.

In addition, since the proposal was published, the Halogenated Solvents Industry Alliance has submitted a citizen petition that states that manufacturers of cosmetics in the United States have already reformulated their hair sprays to remove methylene chloride on their own initiative, and that there is practically no use of methylene chloride in cosmetics in this country. In a letter dated November 30, 1988, FDA has been told that one firm has resumed using methylene chloride in certain aerosol cosmetics. Notwithstanding the cost to this firm of converting production back to its methylene chloride-free formulations, the agency finds that the costs of prohibiting the use of methylene chloride in hair spray are essentially negligible. The agency has received no other relevant information on the economic impact of this action.

The agency has previously considered the environmental effects of this rule as announced in the proposed rule (50 FR 51551). No new information or comments have been received that would affect the agency's previous determination that there is no significant impact on the human environment and that an environmental impact statement is not required. The information that use of methylene chloride in cosmetics has essentially ceased serves to reinforce this finding of no significant impact.

XI. References

The following references have been placed on display in the Dockets Management Branch, Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Memorandum of Meeting of Advisory Panel to the National Cancer Institute on the proposed methylene chloride epidemiology study, June 10, 1987
2. Maltoni, C., Food Solvents Workshop I: Methylene Chloride, Nutrition Foundation, Bethesda, MD., pp. 67-75 and 92-95, March 8 and 9, 1984.
3. Memorandum of August 22, 1985, by C. Lin, Division of Toxicology, FDA.
4. International Agency for Research on Cancer, "Dichloromethane, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, 41:43-85, 1986.
5. National Toxicology Program, "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) in F344/N Rats and B₆C₃F₁ Mice (Inhalation Studies), NTP TR 306, January 1986.

6. Haseman, J.K., et al., "Neoplasms Observed in Untreated and Corn Oil Gavage Control Groups of F344/N Rats and (C57BL/6N X C3H/Hen) F1 (B₆C₃F₁) Mice, *Journal of the National Cancer Institute*, 75:975-984, 1985.

7. Cancer Assessment Committee, Memorandum of Conferences, "Methylene Chloride, January 20, 1983, August 8, 1984, and June 13, 1985.

8. Memorandum of April 23, 1985, by the Quantitative Risk Assessment Committee, FDA.

9. Hext, P.M., J. Foster, and S.W. Millward, "Methylene Chloride (Dichloromethane): 10 Day Inhalation Toxicity Study to Investigate the Effects on Rat and Mouse Liver and Lungs, January 1986.

10. Green, T., et al., "Methylene Chloride (Dichloromethane): The Effects of Exposure to 4000 ppm on Mouse Lung Enzymes, October 1987

11. Witschl, H., and W.M. Haschek, "Cells of Origin of Lung Tumors in Mice, *Journal of the National Cancer Institute*, 70:991, 1983.

12. Beer, D.G., and A.M. Malkinson, "Genetic Influence on Type 2 or Clara Cell Origin of Pulmonary Adenomas in Urethane-treated Mice, *Journal of the National Cancer Institute*, 75:963-967, 1985.

13. Memorandum of October 27, 1986, by V.C. Dunkel, Genetic Toxicology Branch, FDA, with attachments and references.

14. Memoranda of January 5, 1987 and May 20, 1986, by G. Cramer, Regulatory Food Chemistry Branch, FDA.

15. Andersen, M.E., et al., "Physiologically Based Pharmacokinetics and the Risk Assessment Process for Methylene Chloride, preprint, January 19, 1986. (Since published in *Toxicology and Applied Pharmacology*, 67:185-205, 1987.)

16. Reitz, R.H., et al., "Incorporation of In Vitro Enzyme Data into the PB-PK Model for Methylene Chloride (CH₂Cl₂): Implications for Risk Assessment, preprint, dated 4/18/88. (Since published in *Toxicology Letters*, 43:97-116, 1988.)

17. Green, T., et al., "Methylene Chloride (Dichloromethane): Human Risk Assessment Using Experimental Animal Data, May 1988.

18. Green, T., et al., "Methylene Chloride (Dichloromethane): In Vivo Inhalation Pharmacokinetics and Metabolism in F344 Rats and B₆C₃F₁ Mice, September 1986.

19. Green, T., J.A. Nash, and G. Mainwaring, "Methylene Chloride (Dichloromethane): In Vitro Metabolism in Rat, Mouse and Hamster Liver and Lung Fractions and in Human Liver Fractions, September 1986.

20. Reitz, R.H., A.L. Mendrala, and A.M. Schumann, "Methylene Chloride-Glutathione S-Transferase Studies: In Vitro Experiments in Humans, Mice, Rats, and Hamsters, July 1987

21. Green, T., W.M. Provan, and N. Gowans, "Methylene Chloride (Dichloromethane): In Vivo Inhalation Pharmacokinetics in B₆C₃F₁ Mice (Using Stable Isotopes) and F344 Rats, October 1987

22. Green, T., J.A. Nash, and S.J. Hill, "Methylene Chloride (Dichloromethane): Glutathione-S-Transferase Metabolism In

Vitro in Rat, Mouse, Hamster and Human Liver Cytosol Fractions, October 1987

23. Memorandum of June 27, 1984, by V. Frankos, Division of Toxicology, FDA.

24. Gargas, M.L., H.J. Clewell III, and M.E. Andersen, "Metabolism of Inhaled Dihalomethanes In Vivo: Differentiation of Kinetic Constants for Two Independent Pathways, *Toxicology and Applied Pharmacology*, 82:211-223, 1986.

25. Memoranda of December 19, 1986, by the Quantitative Risk Assessment Committee; of December 23, 1986, by R. Brown, Division of Mathematics; and of December 19, 1988, by the Quantitative Risk Assessment Committee, FDA.

26. European Chemical Industry Ecology and Toxicology Centre, "Technical Report No. 26: The Assessment of Carcinogenic Hazard for Human Beings Exposed to Methylene Chloride, Brussels, January 1987

27. Friedlander, B.R., T. Hearne, and S. Hall, "Epidemiologic Investigation of Employees Chronically Exposed to Methylene Chloride: Mortality Analysis, *Journal of Occupational Medicine*, 20:657-666, 1978.

28. Hearne, F.T., and B.R. Friedlander, "Follow-up of Methylene Chloride Study, *Journal of Occupational Medicine*, 23:660, 1981.

29. Hearne, F.T., et al., "Methylene Chloride Mortality Study: Dose-Response Characterization and Animal Model Comparison, *Journal of Occupational Medicine*, 29:217-228, 1987

30. Memorandum of December 2, 1985, by L. Tollefson, Epidemiology and Clinical Toxicology Unit, FDA.

31. Memoranda of November 10, 1986 and August 27, 1987, by the Quantitative Risk Assessment Committee, FDA.

32. Tollefson, L., et al., "Human and Animal Risk Comparisons, *Journal of Occupational Medicine*, 30:18-19, 22, 1988.

33. Shannon, H.S., et al., "Cancer Morbidity in Lamp Manufacturing Workers, Preprint.

34. Memorandum of July 22, 1987, by L. Tollefson, Epidemiology and Clinical Toxicology Staff, FDA.

35. Wilbourn, J.D., et al., "Response of Experimental Animals to Human Carcinogens: An Analysis Based upon the IARC Monographs Programme, *Carcinogenesis*, 7:1853-1863, 1986.

36. Wilbourn, J.D., et al., "Identification of Chemicals Carcinogenic to Man, *Toxicologic Pathology*, 12:397-399, 1984.

37. Tomatis, L., "The Predictive Value of Rodent Carcinogenicity Tests in the Evaluation of Human Risks, *Annual Review of Pharmacology and Toxicology*, 19:511-530, 1979.

38. International Agency for Research on Cancer, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, 41:13-32 (preamble), 1986.

XII. Agency Action

FDA has evaluated the comments on the proposal of December 18, 1985, the new information submitted with the comments, and the information already in the agency's files.

FDA believes that the evidence establishes that methylene chloride is a poisonous or deleterious substance, and that its use in cosmetic products may render those products injurious to users.

Under section 601(a) of the act (21 U.S.C. 361(a)), a cosmetic is deemed to be adulterated "(i) if it bears or contains any poisonous or deleterious substance which may render it injurious to users under the conditions of use prescribed in the labeling thereof, or, under such conditions of use as are customary or usual. Therefore, FDA concludes that cosmetics that contain methylene chloride are adulterated under section 601(a) of the act, and the agency is consequently prohibiting the use of methylene chloride in cosmetic products.

FDA has been informed that, except for one firm that has resumed use of methylene chloride in aerosol cosmetics, the use of methylene chloride in manufacturing hair sprays has virtually ceased in the United States. The agency believes, however, that a regulation is necessary to ensure that all hair spray manufacturers cease using methylene chloride, that hair sprays containing methylene chloride are not imported into this country, and that no new hair sprays or other cosmetics using methylene chloride as an ingredient are introduced into the market.

This prohibition of the use of methylene chloride in cosmetics is effective August 28, 1989. This effective date applies to the initial introduction of products, and the initial delivery of products for introduction, into interstate commerce.

List of Subjects in 21 CFR Part 700

Cosmetics, Packaging and containers.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Part 700 is amended as follows:

PART 700—GENERAL

1. The authority citation for 21 CFR Part 700 is revised to read as follows:

Authority: Secs. 601, 602, 701(a), 704, 52 Stat. 1054 as amended, 1055, 67 Stat. 477 as amended (21 U.S.C. 361, 362, 371(a), 374); 21 CFR 5.10, 5.11.

2. A new § 700.19 is added to Subpart B to read as follows:

§ 700.19 Use of methylene chloride as an ingredient of cosmetic products.

(a) Methylene chloride has been used as an ingredient of aerosol cosmetic products, principally hair sprays, at concentrations generally ranging from 10 to 25 percent. In a 2-year animal

inhalation study sponsored by the National Toxicology Program, methylene chloride produced a significant increase in benign and malignant tumors of the lung and liver of male and female mice. Based on these findings and on estimates of human exposure from the customary use of hair sprays, the Food and Drug Administration concludes that the use of methylene chloride in cosmetic products poses a significant cancer risk to consumers, and that the use of this ingredient in cosmetic products may render these products injurious to health.

(b) Any cosmetic product that contains methylene chloride as an ingredient is deemed adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act.

Dated: January 12, 1989.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 89-15355 Filed 6-28-89; 8:45 am]

BILLING CODE 4160-01-M

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 81

[FRL-3607-6]

Designation of Areas for Air Quality Planning Purposes: Various States

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: By this rule, EPA is amending the Title 40, Chapter I, Part 81 of the Code of Federal Regulations for the states of Alaska, Idaho, Oregon, and Washington in order to clarify that the attainment and unclassifiable areas are designated on the basis of air quality control regions (AQCRs), or portions thereof, rather than the "entire state" or "remainder of state" as currently listed in some cases. No changes to the attainment status of any area are made by this rule. This action is being taken to ensure that the attainment and unclassifiable area designations for these four states conform with the requirements of section 107(d) of the Clean Air Act.

EFFECTIVE DATE: June 29, 1989.

ADDRESSES: Copies of the materials submitted to EPA may be examined during normal business hours at: Air Programs Branch, Docket 10A-89-7 Environmental Protection Agency, 1200 Sixth Avenue, AT-082, Seattle, Washington 98101.

FOR FURTHER INFORMATION CONTACT: David C. Bray, Air Programs Branch, Environmental Protection Agency, 1200 Sixth Avenue, AT-082, Seattle, Washington 98101. Telephone: 206-442-4253 FTS: 399-4253.

SUPPLEMENTARY INFORMATION:

I. Introduction

Under section 107(d) of the Clean Air Act, each air quality control region (AQCR), or portion thereof, is to be identified as to whether it meets or does not meet each national primary and secondary ambient air quality standard, or whether there is insufficient data to be so classified. Each state submitted a list of areas to EPA in late 1977 or early 1978, and EPA published a compilation of these "attainment," "nonattainment," and "unclassifiable" areas in the Federal Register on March 3, 1978 (43 FR 8962).

In general, the March 3, 1978 Federal Register listed areas by AQCRs or portions of AQCRs (e.g., counties or cities). However, for the attainment or unclassifiable listings, EPA sometimes condensed the listing, indicating only that the "entire state," or the "remainder of state," was "attainment" or "unclassifiable" for a specific pollutant. EPA expected that, for Clean Air Act purposes, it would be understood that each AQCR represented a separate "attainment" or "unclassifiable" area in accordance with section 107(d).

The "attainment" or "unclassifiable" areas are important to the prevention of significant deterioration (PSD) program under Part C of the Clean Air Act, because they define the "baseline areas" within which the PSD "increments" are applicable. In recent years, some confusion has arisen with regard to the PSD "baseline areas" in states for which the "attainment" and "unclassifiable" areas are listed as the "entire state" or the "remainder of state."

In order to clearly specify the "attainment" and "unclassifiable" areas in accordance with the requirements of section 107(d), EPA is today amending portions of Title 40, Chapter I, Part 81 of the Code of Federal Regulations (Designations of Areas for Air Quality Planning Purposes) for the states of Alaska, Idaho, Oregon, and Washington. Specifically, EPA is replacing each "entire state" or "remainder of state" entry with AQCR-specific listings in order to clarify that the "attainment" and "unclassifiable areas" are designated on the basis of air quality control regions (AQCRs), or portions thereof. This action does not change the