Washington, DC 20204
(202) 245-3117 RIN: 0905-AB67

Proposed Rule Stage

RISK ASSESSMENT POLICY FOR REGULATING CARCINOGENIC IMPURITIES IN FOOD AND COLOR ADDITIVES

Problem To Be Solved

Many food additives and color additives that are not themselves carcinogenic or otherwise unsafe contain minor amounts of carcinogenic impurities. Before 1982, the Agency generally considered that a safe level could not be established for a food or color additive that contains a carcinogenic impurity. Consequently, the Agency, with few exceptions, prohibited their use.

On April 2, 1982, the Agency published an advance notice of proposed rulemaking that announced a new policy for authorizing the use of noncarcinogenic additives containing carcinogenic impurities, so long as the risk presented by these impurities is insignificant, as determined by scientific risk assessment procedures (47 F.R. 14465). On that date, the Agency also announced its first approval under the policy: the permanent listing of D&C Green No. 6, a color additive for use in externally applied drugs and cosmetics. Since then, the Agency has approved a number of other food and color additives based on the new policy.

The new policy has been applied on an additive-by-additive basis. In 1982 (47 F.R. 24278-24284), the Food and Drug Administration (FDA) applied this policy in listing D&C Green No. 5. When this action was challenged, it was upheld by the United States Sixth Circuit Court of Appeals (*Scott* v. *FDA*, 728 F. 2d 322 (6th Cir. 1984)).

The FDA does not have procedural regulations that provide for the use of the new policy and standard criteria for its application. As a result, the Agency must explain the policy each time it is applied, and the policy is subject to *de novo* review if an Agency action is challenged in court. Therefore, the Agency plans to issue procedural regulations for the new policy, as discussed below.

The Agency, however, will continue to apply the policy on an additive-by-additive basis until the planned procedural regulations are issued. Vinyl chloride copolymers are among the additives containing carcinogenic impurities on which the Agency plans to take regulatory action prior to issuing procedural regulations for the policy. The Agency applied this policy in listing the acrylonitrile/styrene copolymers (September 19, 1984 (49 F.R. 36635)).

Need For Federal Solution

Food additives and color additives are subject to the food additive and color additive provisions of the Federal Food, Drug, and Cosmetic Act. Such additives cannot be used unless the Agency issues regulations authorizing their use. This may be done only for those food and color additives that have been shown to be safe.

Approach

The Agency plans to submit to the Secretary procedural regulations that would state criteria for authorizing the use of those noncarcinogenic additives that contain carcinogenic impurities at levels that present an insignificant risk. This regulatory action is consistent with the Administration's regulatory principles because: (1) the approach uses risk assessment procedures; (2) the potential benefits exceed the potential costs; (3) reviews of and decisions on new products will be made more swiftly and will be based on standards that are clearly defined in advance; and (4) safety will not be compromised.

Until the planned procedural regulations are issued, the Agency will continue to apply and defend the policy on an additive-by-additive basis. Although, as an alternative approach, an additive-by-additive approach would eliminate the need for a procedural regulation to be issued, it is a less efficient use of Agency resources. Further, if there are more court challenges to approvals using the policy, each case would require *de novo* review on the merits. Also, less guidance would be available for industry petitioners to use in developing new products.

Next Steps

Legal deadline: None.

Milestones:

Action	*Date*
NPRM	February 1987
Final Action	February 1988

Agency Contact

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CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS; RETROSPECTIVE REVIEW

Problem To Be Solved

On September 19, 1980, Public Law 96-354, the Regulatory Flexibility Act, was enacted. Section 610 of the Act requires that each Federal agency publish in the *Federal Register* a plan for the periodic review of both existing and new rules issued by the agency

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 74, 81, and 82

[Docket No. 83C-0102]

Listing of D&C Orange No. 17 for Use in Externally Applied Drugs and Cosmetics

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is permanently listing D&C Orange No. 17 as a color additive for use in externally applied drugs and cosmetics. FDA is taking this action because it has concluded that the use of this color additive in externally applied drugs and cosmetics is safe within the meaning of section 706 of the Federal Food, Drug, and Cosmetic Act. This action responds to a petition filed by the Cosmetic, Toiletry and Fragrance Association, Inc.

DATES: Effective September 9, 1986, except as to any provisions that may be stayed by the filing of proper objections; objections by September 8, 1986. FDA will publish notice of the objections that the agency has received or lack thereof in the Federal Register.

ADDRESS: Written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATI N CONTACT: Gerad L. McCowin, Center for Food Safety and Applied Nutrition (HFF-330), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5676.

SUPPLEMENTARY INFORMATION:

I. Introduction

In 1960, Congress passed the Color Additive Amendments (the amendments). In *Certified Color Mfg. Ass'n* v. *Mathews*, 543 F.2d 284, 286-287 (D.C. Cir. 1976), the United States Court of Appeals for the District of Columbia Circuit explained the purpose of this legislation:

> The Color Additive Amendments of 1960 reflect a Congressional and administrative response to the need in contemporary society for a scientifically and administratively sound basis for determining the safety of artificial color additives, widely used for coloring food, drugs, and cosmetics. The Amendments reflect a general unwillingness to allow widespread use of such products in the absence of scientific information on the effect of these products on the human body. The previously used system had some glaring deficiencies, and the 1960 Amendments were designed to overcome them. * * *
>
> [Footnotes omitted.]

As amended, the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) (the act) provides in section 706(a) (21 U.S.C. 376(a)) that a color additive will be deemed unsafe for use in food, drugs, cosmetics, and some medical devices unless FDA has issued a regulation permanently listing that color additive for its intended use. FDA will issue such a regulation only if it has been presented with data that establish with reasonable certainty that no harm will result from the use of the color additive. The burden of presenting such data is on the person who is seeking approval of the use of the additive.

In passing the amendments, Congress provided for the provisional listing of the color additives in use at that time, pending completion of the scientific investigations needed for a determination about the safety of these additives (section 203(b) of the transitional provisions of the amendments, Title II, Pub. L. 86-618, 74 Stat. 404-407 (21 U.S.C. 376, note)). Section 81.1 (21 CFR 81.1) of the agency's color additive regulations enumerates those color additives that are still provisionally listed. Among them is D&C Orange No. 17 for use in

externally applied drugs and cosmetics. Because D&C Orange No. 17 was in use at the time the amendments were enacted, it had been provisionally listed for drug and cosmetic use in the Federal Register of October 12, 1960 (25 FR 9759).

II. Regulatory History

A. The Color Additive

D&C Orange No. 17 is principally 1-[(2,4-dinitrophenyl)azo]-2-naphthalenol (CAS Reg. No. 3468-63-1). Although it is identified in § 82.1267 (21 CFR 82.1267) as 1-(2,4-dinitrophenylazo)-2-naphthol, these two descriptions are synonymous.

B. Color Additive Petition

D&C Orange No. 17 is the subject of a color additive petition (CAP 9C0090) that was submitted on April 14, 1969, by the Toilet Goods Association, Inc. (now the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), 1110 Vermont Ave. NW., Washington, DC 20005). FDA published a notice of filing of the petition in the Federal Register of August 6, 1973 (38 FR 21199). The petition, filed under the provisions of section 706 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 376), requested the permanent listing of D&C Orange No. 17 for coloring lipsticks, ingested drugs, and externally applied drugs and cosmetics.

In a letter dated May 14, 1974, the petitioner requested that the petition be amended to include listing D&C Orange No. 17 for eye-area use. FDA published an amended filing notice for the petition in the Federal Register of March 5, 1976 (41 FR 9584), to include the listing of D&C Orange No. 17 for eye-area use. FDA notified the petitioner by letters dated May 14, 1976, August 15, 1977, and August 4, 1978, of the need for data to support the use of D&C Orange No. 17 in cosmetics intended for use in the area of the eye. In a letter dated October 24, 1978, FDA advised the petitioner to consider withdrawing that portion of the petition that sought approval of the use of D&C Orange No. 17 in cosmetics intended for use in the area of the eye because it appeared that the required data from eye-area studies would not be readily available.

The petitioner did not submit the required data. Therefore, in a notice published in the Federal Register of April 1, 1983 (48 FR 14045), FDA announced that that portion of the petition relating to the listing of D&C Orange No. 17 for eye-area use was withdrawn without prejudice to a future filing. Eye-area use of D&C Orange No. 17 had never been provisionally listed.

In the Federal Register of February 4, 1977 (42 FR 6991), FDA published revised provisional regulations which required new chronic toxicity studies on 31 color additives, including D&C Orange No. 17, as a condition for continued provisional listing of these additives. FDA required the new chronic studies because the toxicity studies that the petitioners had submitted were deficient in several respects. FDA described these deficiencies in the Federal Register of September 23, 1976 (41 FR 41863):

1. Many of the studies were conducted using groups of animals i.e., control and those fed the color additive, that are too small to permit conclusions to be drawn on the chronic toxicity or carcinogenic potential of the color. The small number of animals used does not, in and of itself, cause this result, but when considered together with the other deficiencies in this listing, does do so. By and large, the studies used 25 animals in each group; today FDA recommends using at least 50 animals per group.
2. In a number of the studies, the number of animals surviving to a meaningful age was inadequate to permit conclusions to be drawn today on the chronic toxicity or carcinogenic potential of the color additives tested.
3. In a number of the studies, an insufficient number of animals was reviewed histologically.
4. In a number of the studies, an insufficient number of tissues was examined in those animals selected for pathology.
5. In a number of the studies, lesions or tumors detected under gross examination were not examined microscopically.

In the February 4, 1977, order, FDA postponed the closing date for the provisional listing of D&C Orange No. 17 until January 31, 1981, for the completion of the new chronic toxicity studies. In the Federal Register of March 27, 1981 (46 FR 18958), the agency established a new closing date of March 31, 1983, for the completion of the chronic toxicity studies and the submission of data to FDA on a prescribed schedule.

In the Federal Register of April 1, 1983 (48 FR 13976), FDA announced that the provisional listing of the use of D&C Orange No. 17 for coloring ingested drugs and cosmetics had expired (48 FR 13976) and denied that portion of the petition that requested the listing of D&C Orange No. 17 for ingested drug and cosmetic uses (48 FR 14045). FDA took the latter action because it concluded, on the basis of the animal experiments that had been performed as a condition of the provisional listing of D&C Orange No. 17, that the color additive was carcinogenic when administered in the diet of laboratory animals. As a result of these actions, D&C Orange No. 17 could not be added to ingested drugs and cosmetics after April 1, 1983. D&C Orange No. 17 remained provisionally listed for use in externally applied drugs and cosmetics.

As discussed in the Federal Register of April 1, 1983 (48 FR 14047), the petitioner continued to seek permanent listing for the use of this color additive in external cosmetic and drug products that are not subject to incidental ingestion. On March 22, 1983, CTFA submitted preliminary results of a percutaneous absorption study of D&C Orange No. 17. Another CTFA submission, dated April 15, 1983, included a review and analysis of scientific studies, including an assessment of the risk from the use of D&C Orange No. 17 in external cosmetic and drug products, a final report on percutaneous absorption of D&C Orange No. 17, and a discussion of the legal issues raised by external use of this color additive. The agency agreed to review these submissions before reaching a conclusion on the safety of the use of D&C Orange No. 17 in externally applied drugs and cosmetics. Because its review of the CTFA submissions and of the scientific and legal issues raised by this matter took longer than the agency anticipated, FDA had to extend the provisional listing of this color additive on a number of occasions. The agency established the current closing date of August 6, 1986, for the provisional listing of D&C Orange No. 17 for use in externally applied drugs and cosmetics by a rule published in the Federal Register of June 6, 1986 (51 FR 20786). In that notice, the agency also announced its decision to permanently list the color additive for its external drug and cosmetic uses. The discussion that follows sets forth the basis for that decision and the agency's conclusion that the use of D&C Orange No. 17 as a color additive in externally applied drugs and cosmetics is safe within the meaning of section 706 of the act.

C. Citizen Petition Filed by Public Citizen Health Research Group

On December 17, 1984, the Public Citizen Health Research Group (Public Citizen) petitioned FDA to ban the use of the color additives that remained provisionally listed. On January 22, 1985, Public Citizen filed a complaint in the District Court for the District of Columbia seeking the same relief. Public Citizen alleged that, by continuing to provisionally list the color additives, including D&C Orange No. 17, FDA had violated the Color Additive Amendments to the act, as well as those provisions of the Administrative Procedure Act (5 U.S.C. 706(1)) that

pertain to unreasonable delay of agency action. Public Citizen sought to enjoin FDA from using the provisional list or any other means to allow the marketing of the provisionally listed color additives.

On June 21, 1985, the Commissioner of Food and Drugs sent to Public Citizen a detailed response to the petition. In his response the Commissioner carefully reviewed and discussed the arguments and information submitted in support of the petition. The Commissioner concluded that the public health would not be endangered by the continued marketing of the color additives while scientific, legal, and policy issues were addressed and, therefore, the Commissioner denied the petition.

On February 13, 1986, Judge Stanley S. Harris granted FDA's motion for summary judgment and dismissed Public Citizen's complaint. *Public Citizen et al.* v. *DHHS, et al.*, No. 85-1573 (D.D.C. February 13, 1986). Public Citizen has appealed Judge Harris' decision.

III. Review of Provisionally Listed Color Additives by a Scientific Review Panel

In the proposal to extend the closing dates for the provisional listing of certain color additives, including D&C Orange No. 17 (50 FR 26377, June 26, 1985), FDA announced that the Commissioner had established a scientific review panel (panel) of Public Health Service scientists to evaluate data and report on the risk assessment issues presented by the use of six color additives: D&C Red No. 8, D&C Red No. 9, D&C Red No. 19, D&C Red No. 37, D&C Orange No. 17, and FD&C Red No. 3.

FDA asked the panel to consider several scientific issues that had been raised by FDA scientists about whether a reliable assessment of the risk from the use of these additives could be conducted. Specifically, one issue was whether, for each additive, unidentified contaminants, rather than the principal color component, could be responsible for the observed carcinogenic effects in animal testing, and whether any such unknown impurities or components may be absorbed through the skin to a greater or lesser extent than other parts of the additive. The panel was charged with examining this impurities issue and further with addressing the issue of whether a risk assessment calculation could be made from the available data, and, if so, whether the risk assessments before the agency were properly calculated.

In the Federal Register of March 6, 1986 (51 FR 7856), FDA announced the availability of the final report of the panel. The report is entitled "Report of the Color Additive Scientific Review Panel, September 1985, Docket No. 86N-0039." A copy of the report is available to the public for review at the Dockets Management Branch (address above). Requests for copies of the report should be identified with Docket No. 86N-0039.

In the report, the panel concluded that the risk assessments submitted by the petitioner for several of the color additives, including D&C Orange No. 17, are consistent with current acceptable usages in risk assessment. The panel also concluded that legitimate issues with regard to impurities had been raised but could be addressed by making reasonable and appropriate assumptions about the possible influence that such impurities might have. The panel concluded that the range of lifetime risk presented by external exposure to D&C Orange No. 17 was extremely low. The report of the panel was also submitted to peer review and subsequently published in *Risk Analysis*, 6:2:117-154, 1986, hereby broadly providing the risk analysis assessment to the scientific community. These findings will be discussed in greater detail below.

IV. Overview of the Final Rule

FDA has evaluated all the available evidence regarding the safety of D&C Orange No. 17. Based upon this evaluation, FDA finds that the use of D&C Orange No. 17 in externally applied drugs and cosmetics is safe. Although the external uses involve, based on conservative statistical analysis, a theoretical carcinogenic risk, the agency finds that this risk is so trivial as to be effectively no risk at all. For these reasons, the agency has decided to permanently list these uses of D&C Orange No. 17.

The remainder of this document describes the information and advice relied upon by the agency in reaching its conclusion as to the safety of D&C Orange No. 17 as a color additive for externally applied drugs and cosmetics. First, the agency evaluates the available data resulting from toxicology testing of D&C Orange No. 17 and then discusses CTFA's safety evaluation of these data. Next the agency deals with CTFA's arguments and questions concerning the relevance of the toxicology tests to the determination of the safety of the external drug and cosmetic uses of D&C Orange No. 17. In the following section, FDA discusses CTFA's assessment of the extent of human exposure resulting from the external drug and cosmetic uses of D&C Orange No. 17.

In the remaining sections, FDA discusses CTFA's low dose carcinogenic risk assessment approach, the report of the panel, and the panel's conclusions regarding the propriety of relying upon the available data to conduct risk assessments for use by a government regulatory agency. The final section discusses the agency's reliance on the *de minimis* doctrine to reach the conclusion that the proscriptions of the Delaney Clause should not be invoked in this matter.

V. Toxicology Testing of D&C Orange No. 17

A. Discussion: Summary of Studies Submitted by CTFA

To establish that D&C Orange No. 17 is safe for use in drugs and cosmetics, CTFA submitted reports on a number of animal toxicity studies for the color additive. Among these studies were chronic and subchronic feeding studies in dogs and rats, a three-generation reproduction study in rats, teratology studies in rats and rabbits, a dermal study in rabbits, and an 18-month skin painting study in mice. These studies did not produce any evidence that the use of this color additive, for the petitioned uses, would be unsafe.

The 18-month skin painting study, which is relevant to the use of D&C Orange No. 17 in externally applied drugs and cosmetics, was performed using 2 groups, each consisting of 50 male and 50 female Swiss-Webster mice. One group, the controls, was treated with distilled water, while the test group was treated with D&C Orange No. 17 applied as a 1 percent aqueous suspension, in terms of the pure color. Treatment consisted of the application of 0.1 milliliter of the test material to the clipped backs of each animal two times per week. Observations were made daily for mortality and twice weekly for gross toxicity.

Animals that died, those sacrificed as being moribund, and those surviving the 18-month study were autopsied. Tissues sectioned and examined microscopically included skin and grossly abnormal organs and tissues from 27 female control animals, 25 male control animals, and all animals in the experimental group. Complete pathology was performed on five males and five females from the control animals and five males and five females from the tested group.

Results from the treated and untreated animals were essentially similar, as were survival patterns. Tissue masses were observed in the areas of repeated dermal application of the color in two mice. One was a wartlike growth that could not be located in the fixed tissue and the other was identified as a

papilloma. Two control animals were also found to have lesions in or beneath the skin. The lesions were identified as a subcutaneous, undifferentiated sarcoma and the second as a subcutaneous anaplastic osteogenic sarcoma. Dermal effects such as acanthosis, hyperkeratosis, and dermatitis were somewhat increased in the experimental group when compared to the controls.

Although no evidence of compound-related neoplastic responses was found in these skin painting or chronic feeding studies, FDA concluded that the sensitivity of the chronic feeding studies was insufficient under current standards to provide the requisite demonstration of safety for ingested use. Therefore, in the February 4, 1977, order, FDA required additional chronic feeding studies on D&C Orange No. 17. The studies were conducted for the petitioner at Bio/dynamics, Inc., East Millstone, NJ. These studies included a long-term feeding study in mice and a chronic toxicity/carcinogenicity study, with in utero exposure to D&C Orange No. 17, in rats. The final reports for these studies (CAMF #9, Entries 510, 511, 512) were received by the agency on March 31, 1982.

The new long-term chronic studies represent current state-of-the-art toxicological testing. The protocols for these studies have benefited from knowledge of deficiencies in previously conducted carcinogenesis bioassays and other chronic toxicity protocols. The use of large numbers of animals of both sexes, pilot studies to determine maximum tolerated dosages, two control groups (thereby effectively doubling the number of controls), and in utero exposure in one of two species tested significantly increases the power of these tests to detect dose-related effects. The studies were designed and conducted in compliance with FDA's good laboratory practice regulations (21 CFR Part 58) and were subject to inspections by FDA officials during their course.

B. Evaluation of the Long-Term Studies

1. Long-Term Feeding Study in Rats

The long-term feeding study in rats included in utero exposure to D&C Orange No. 17. Charles River Albino (CD) rats (parental animals) were randomly assigned (60 males and 60 females per group) and mated to produce the F_1 generation. D&C Orange No. 17 was mixed with standard laboratory chow and fed ad libitum to the parental animals during their mating and gestation period and to their offspring (the F_1 generation animals) during the long-term feeding study. Two separate groups of rats served as controls.

The petitioner, in meeting with FDA on September 12, 1977, discussed the adequacy of the protocol for this chronic feeding study. FDA's scientists indicated that the proposed dosage levels (i.e., 0.00, 0.02, 0.05, and 0.10 percent) were too low. On the basis of data from earlier studies on D&C Orange No. 17, FDA's scientists concluded that survival and weight data suggested that lifetime studies could be successfully carried out in rats using 1.0 percent as the maximum dosage level. The agency, therefore, asked the petitioner to conduct an additional rat chronic feeding study with a 1.0 percent dosage level of D&C Orange No. 17 (Ref. 10). This study was carried out with the same strain of rats and with the same experimental design as the original study. It included a treatment group and a concurrent control group.

Seventy F_1 rats of each sex, obtained from the reproduction phase of the study, were randomly selected and distributed into dosage groups similar to those described above for their parental animals and were used for the chronic feeding phase of the study (26 months for males and 30 months for females). Survival and body weights of female rats from the chronic feeding phase were unaffected by treatment. However, treated male rats in this phase exhibited decreased survival as well as decreased body weights at the highest dose (1.0 percent diet) (Ref. 1). Except for discoloration of the urine, there were no hematological or clinical findings that could be ascribed to treatment. Increased deposition of pigment in the spleen of female rats was noted in the 1.0 percent group.

Among female rats, at the 1.0 percent dietary level of D&C Orange No. 17, there was a marked and statistically significant increase in animals with hepatocellular tumors (neoplastic nodules and carcinomas combined) compared to the concurrent control group animals (21/70 in the 1.0 percent dose group versus 3/70 in the concurrent control group, $p = 0.0001$, prevalence analysis; 70 is the number of animals entered into the study). The denominators reflect the number of livers for which tissue was available for microscopic examination, including the 10 animals in each group which were interim sacrificed after approximately 1 year of treatment according to protocol. They represent the number of livers examined by FDA pathologists. The prevalence statistical analysis, however, is a time-adjusted test. It takes into account deaths, including interim sacrifice deaths, that are incidental to the finding of liver neoplasms. The incidence of animals with non-neoplastic liver lesions (foci of cellular alteration) was also increased among female rats in the 1.0 percent dose group when compared to the control group.

Additionally, multiple hepatocellular tumors (neoplastic nodules) were noted only in the 1.0 percent D&C Orange No. 17 treated group females. Moreover, the number of animals with multiple occurrences of foci of cellular alteration (non-neoplastic lesion) and of animals that had multiple classifications, i.e., foci of cellular alteration and neoplastic nodules, present in the same microscopic section of liver was higher among treated group females (1.0 percent dose group) than in the concurrent control group. The 1.0 percent dose group females had increased liver weights as well. The liver data in the 1.0 percent study indicate a clear-cut treatment-related effect in the occurrence of hepatocellular tumors in female rats as a result of the administration of D&C Orange No. 17. Liver weights relative to body weights were also increased in both male and female rats that received 0.10 percent D&C Orange N . 17 in the diet, indicating further that the liver is the target organ for D&C Orange No. 17 toxicity.

The petitioner provided historical control data for hepatocellular tumors in Charles River Albino female rats from 12 separate control groups from studies conducted at Bio/dynamics, Inc. The average incidence of hepatocellular tumors (neoplastic nodules and carcinomas combined) was 9.4 percent. In contrast, the incidence of hepatocellular tumors in the high-dosage (1.0 percent) group was 30 percent, far exceeding the average spontaneous incidence.

Thus, the long-term feeding exposure of Charles River CD Albino rats to a 1.0 percent dose level of D&C Orange No. 17 produced the carcinogenic effect of a statistically significant increase in the number of female rats with hepatocellular neoplasms compared to the control groups.

2. Long-Term Feeding Study in Mice

Charles River CD-1 mice of both sexes were randomly assigned to one of three treatment groups receiving D&C Orange No. 17 in the diet at concentrations of 0.025, 0.25, and 1.0 percent or to one of two control groups and fed the test diets for approximately 23 months for the males and 25 months for the females. The selection of these

dosage levels was based on the results of a 90-day rangefinding study.

The incidence of hepatocellular neoplasms (adenomas and carcinomas) among male mice was increased in a dose-related manner ($p=0.00004$, trend test). The incidence of hepatocellular neoplasms in male mice was 8/58 and 8/59 or 16/117 for the two control groups, and 11/58, 13/57, and 19/56 for the low-, medium-, and high-dose groups, respectively. Again, as with the rats, the denominators reflect the number of livers for which tissue was available or was adequate for microscopic examination by FDA pathologists. A few missing and autolyzed tissues account for the less than 60 per group expected from the initial number of animals started on test. The appropriate time-adjusted prevalence analysis was performed on the incidences. A small increase, compared to the corresponding control group animals, in the number of female mice with hepatocellular neoplasms in the mid- and high-dose groups was also reported. Thus, the long-term feeding exposure of Charles River CD–1 mice of D&C Orange No. 17 was associated with a significant dose-related increase in the number of male mice with hepatocellular neoplasms compared to the control groups.

Survival of male mice fed the D&C Orange No. 17 diets was decreased in a dose-related manner ($p=0.0005$, Cox's time-adjusted trend test), but survival of female treated mice apparently was not adversely affected by treatment. Similarly, body weights of high-dose male mice were slightly less than controls, but no effect on body weights of treated female mice was seen.

Also, there was an increase in mortality noted in mid-dose and high-dose males as well as in mid-dose females. Aside from test material coloration of the coats of the treated animals, there were no significant treatment-related effects on general physical condition, body weights, food consumption, or incidence of palpable tissue masses. Mean hemoglobin concentration, hematocrit, and erythrocyte counts were often slightly reduced with concomitant increases in reticulocyte counts relative to control in the high-dose animals.

Microscopic examination revealed pigment deposition in the brain, spinal cord, thyroid, heart, and stomach in all treatment groups as well as in the spleen, cecum, and liver in the males and females in the high-dose group. The neurons of the brain and spinal cord of high-dose males and females were noted to have an increased incidence of neuronal basophilia. This was associated with the intracytoplasmic accumulation of pigment in animals at the high-dose level. High-dose female mice were observed to have an increased incidence of chronic myocarditis.

3. *Related information.* In addition to the results from the long-term feeding studies, D&C Orange No. 17 has been reported to be mutagenic to all standard tester strains of *Salmonella typhimurium* but not in the one mammalian system tested. One of its probable metabolites, 2,4-dinitroaniline, is also mutagenic to all tester strains, and another probable metabolite, 1-amino-2-naphthol, belongs to a chemical class that includes known carcinogens.

C. FDA's Conclusion Regarding the Ingested Uses of D&C Orange No. 17

No significant data base has been developed concerning the toxicity of D&C Orange No. 17 since the agency concluded in the Federal Register of April 1, 1983 (48 FR 14047), that the color additive was a carcinogen when administered in the diet of laboratory animals.

Based on these findings, the agency denied that part of CTFA's petition requesting permanent listing of D&C Orange No. 17 for use in ingested drugs and cosmetics (48 FR 14047; April 1, 1983). The agency also administratively withdrew that part of the petition requesting eye-area use because CTFA had failed to provide data in support of such a use.

VI. CTFA'S Safety Arguments

In its submissions, CTFA presented several arguments that raise questions about the relevance of the ingestion studies to a determination of the safety of the use of D&C Orange No. 17 to color externally applied drugs and cosmetics. In the following sections, the agency reproduces the arguments and its internal evaluation of them.

A. Interpretation of Maximum Tolerated Dose

In the submission dated April 15, 1983, CTFA asserted that the 1.0 percent dose level of the second rat study substantially exceeded the maximum tolerated dose and thus violated the National Cancer Institute (NCI) guidelines for carcinogenicity testing.

The NCI guidelines define the maximum tolerated dose as "the highest dose of a test agent given during the chronic study that can be predicted not to alter the animals' normal longevity from effects other than carcinogenicity" (Ref. 1). The guidelines also state that the maximum tolerated dose "should be the highest dose that causes no more than a 1.0 percent weight decrement, as compared to the appropriate control groups; and does not produce mortality, clinical signs of toxicity, or pathogenic lesions (other than those that may be related to a neoplastic response) that would be predicted to shorten the animals' natural life span" (Ref. 1). The purpose of establishing the maximum tolerated dose is to assure that the test animals are challenged but not killed by the noncarcinogenic toxic effects of high doses of a substance. Early death would obscure any carcinogenic effects of the substance being tested.

The question whether the maximum tolerated dose was exceeded is relevant only to the female rats, among whom the increase in liver neoplasms was found. The feeding of D&C Orange No. 17 at the highest dietary level to these animals had no effect on their survival when compared to the controls. Application of the NCI computer program for tumor/mortality analysis to the female survival data yields a Cox statistic (time-adjusted, continuity corrected) with a probability of 0.32 and a Breslow statistic (time-adjusted) with a probability of 0.19. These numbers indicate that the females' survival was not affected by the feeding of D&C Orance No. 17. Further, no difference in the average body weights was observed between treated and control female rats. In addition, there were no clinical signs of toxicity or postmortem lesions other than those related to the neoplastic response. Therefore, the agency concludes that, for the female rats, the maximum tolerated dose was not exceeded and that CTFA's contention that the study violated NCI guidelines for carcinogenicity testing is not substantiated.

B. Significance of Mouse Liver Tumors

In its April 15, 1983 submission, CTFA questioned the significance of the mouse liver tumors observed in the chronic tests. First, CTFA contended that reliance on the male mouse liver tumors is controversial because many strains of mice have a high incidence of liver tumors and retrovirus infection. Second, CTFA argued that the observed male mouse liver tumors were associated only with severe liver toxicity at the feeding level of 1 percent of the color additive in the diet and that this level exceeded the maximum tolerated dose. Finally, CTFA stated that, in any event, the male mouse liver tumors were statistically significant compared only to the controls in this study but not to the controls in other recent studies, thus suggesting that the tumors were not, in fact, an event worthy of attention

Some members of the scientific community have argued that a compound should not be regarded as carcinogenic if the only evidence of carcinogenicity is an increase in hepatomas in the mouse liver because many inbred mouse strains have a high background incidence of these neoplasms. According to this argument, the tumors indicate the presence of a latent population of initiated tumor cells rather than a carcinogenic effect of the compound.

The liver, because of its location and important role in metabolism, is a frequent target organ for toxic effects of compounds administered by the oral route. Substances absorbed from the gastrointestinal tract reach the liver in amounts much higher than the amounts to which other organs are generally exposed. Metabolic conversion of a substance to a more toxic metabolite often occurs in the liver, and the liver cells are exposed to the highest concentration of the active agent. Thus, hepatotoxic effects may be the only toxic effects observed. For this reason, the agency believes that the liver tumors must be carefully considered. FDA's Cancer Assessment Committee reviewed the data and CFTA's arguments and reached the following conclusions:

CTFA's argument about the high background incidence of liver cancer in mice does not apply to the CD–1 mouse, the strain used in the mouse study. The background incidence of hepatocellular tumors in this strain is low compared to most mouse strains. Moreover, data submitted by CTFA on April 8, 1981, showed the following incidence of tumors in 16 control groups (more than 900 mice of each sex):

	Males	Females
Hepatocellular carcinoma	9.65% ± 4.25%	0.63% ± 1.03%
Hepatocellular adenoma	5.12% ± 3.92%	1.17% ± 1.21%

Thus, the incidence of hepatocellular tumors (carcinomas and adenomas) among male mice in the control groups was about 15 percent. In contrast, the incidence of hepatocellular tumors among male mice in the high-dose group was about 34 percent.

Moreover, CTFA's argument concerning exceeding the maximum tolerated dose is misplaced. The argument is only relevant to the high-dose male mouse group in which the increase in hepatocellular neoplasms was observed. Although body weights and survival of mice in this group were slightly affected, no significant treatment-related effects were observed aside from material coloration of the coats of the animals. As discussed above, the purpose of establishing the maximum tolerated dose is to assure that the test animals are appropriately challenged but are not killed by the noncarcinogenic toxic effects of high doses of the substance. In the absence of any observed significant treatment-related effects other than the hepatocellular neoplasms, the committee concluded that the maximum tolerated dose was not exceeded in the study.

Finally, CTFA's argument concerning the limited statistical significance associated with the male mouse liver tumors was evaluated. In this study with D&C Orange No. 17, the incidence of male mice with hepatocellular tumors was increased in comparison to the concurrent controls at both the mid- and high-dose levels, and the increase was dose related (Trend Test $p=0.00004$). Furthermore, the historical control and concurrent control values are very similar. Consequently, the tumor incidence in treated mice is greater than the historical control values. There is also a dose-related increase in the numbers of male mice with malignant tumors (i.e., hepatocellular carcinomas) (Trend Test $p=0.046$).

The International Expert Advisory Committee to the Nutrition Foundation (Ref. 2) described the following factors as important in determining whether the production of mouse hepatocellular tumors is the result of treatment: (1) Incidence of tumors in treated animals is clearly higher than in concurrent controls; (2) Incidence is also higher than in historical controls or dose related; (3) There is a decrease in time of onset in the treated animals; (4) There is a preponderance of malignant lesions in treated animals compared with the controls; and (5) tumors are observed at other sites in the mouse, or tumors are observed in other species. Each of these conditions was reviewed in the case of D&C Orange No. 17, and, accordingly, the committee concluded that the hepatocellular tumors observed in the male mice were the result of the ingestion of D&C Orange No. 17. (The panel also reviewed available data on the rat and mouse bioassays of D&C Orange No. 17. Although the panel reached different conclusions with respect to the mouse bioassay, this difference is inconsequential, in light of the fact that the rat has been shown to be the most sensitive test species and the 1.0 percent feeding study in rats provides the best data base from which to estimate the likely risks to man presented by exposure to the external uses of D&C Orange No. 17.)

C. Mechanism of Carcinogenicity and Significance of "Benign" Tumors

In its April 15, 1983, submission, CTFA offered the following arguments concerning the significance of benign tumors: "[In the female rat], only the incidence of benign hepatocellular adenomas (neoplastic nodules) was increased. There was no significant increase in the incidence of malignant carcinomas in the treated female. Nor was there any effect in the males fed the same level of color additive. This indicates a very weak effect apparently occurring only at high doses that are toxic to the liver. This suggests an indirect mechanism of neoplasia secondary to toxic damage." (Petitioner's Submission of April 15, 1983, p. 21.)

FDA agrees that the increase in the incidence of malignant hepatocellular carcinomas in the 1.0 percent dose group of the female rat would not be statistically significant if malignant hepatocellular carcinomas alone were considered. However, FDA notes that on the issue of "benign" and "malignant" tumors, a 1979 report of the Interagency Regulatory Liaison Group stated: "Carcinogenic and chronic toxic effects of a chemical on an organ, tissue or cell develop through a series of stages from minimal changes to advanced and possibly fatal end points. The stage reached at any particular time is related to the dose of a substance, the conditions of exposure, the time elapsed since the beginning of exposure and host susceptibility factors. Early lesions that are pathognomonic of a disease process resulting from toxic chemicals should be grouped with more advanced lesions, whether or not the animal has survived long enough for the process to develop to the latest stage." (Ref. 3.)

FDA agrees with this analysis and believes that it is appropriate to combine hepatocellular neoplasms (neoplastic nodules, adenomas, and carcinomas) for analysis because all of these lesions could be concurrent or sequential stages in the neoplastic process (Ref. 4).

In the case of D&C Orange No. 17, the incidence of female rats with benign and malignant hepatocellular tumors (neoplastic nodules and hepatocellular carcinomas, respectively) was analyzed both separately and combined. When a Fisher's Exact Test was applied to compare the incidence of animals with a neoplastic nodule in the 1 percent D&C Orange No. 17 dose group with that of the control group, a p-value of less than 0.01 was found. The agency also did a prevalence analysis, which yielded a

Cox statistic corresponding to a probability of less than 0.001, thereby reinforcing the results of the Fisher's Exact Test. The probability derived from the combined incidence of animals with a neoplastic nodule or a hepatocellular carcinoma was even smaller. This information leads the agency to conclude that D&C Orange No. 17 most likely exhibits a primary effect. CTFA has offered no evidence to the contrary.

CTFA also suggested in its submission that the female rat liver tumors in the 1 percent dose group are caused by an "indirect mechanism of neoplasia secondary to toxic damage * * *." However, CTFA has not submitted any scientific evidence to support such a hypothesis.

D. Percutaneous Absorption Studies With D&C Orange No. 17

On April 15, 1983, CTFA submitted its final report of an in vitro percutaneous absorption study on D&C Orange No. 17. An in vitro percutaneous absorption test is designed to measure the ability of a substance, such as a color additive, to penetrate excised skin under conditions simulating human use. Information on skin penetration is important for determining the systemic exposure to a color additive used in topical applications.

The study was performed, in general, in a satisfactory manner. The test data clearly show that radiolabeled material from D&C Orange No. 17 passes through the skin in small but measurable amounts. Therefore, the agency concluded that some systemic exposure to a portion of the color additive may occur from the use of externally applied drugs and cosmetics containing D&C Orange No. 17.

The assessment of the carcinogenic risk from the use of an externally applied carcinogenic color additive is determined by (1) the amount of color additive applied to the skin and the frequency of application, (2) the concentration of carcinogenic agents in the color additive, (3) the potency of the carcinogenic agents, and (4) the fraction of the applied carcinogenic agents that penetrates the skin.

The risk estimates submitted by CTFA are based on the assumptions (1) that the principal color component is the carcinogenic agent, (2) that the radiolabeled material penetrating skin is representative of the whole color additive, and (3) that 100 percent of the carcinogenic agent is absorbed from the alimentary tract into the blood stream in the animal feeding studies.

FDA's scientists questioned CTFA's assumptions because the argument could be made that a contaminant is responsible for the carcinogenic response. Color additives are not pure substances and normally contain intermediates, subsidiary colors, and other contaminants from intermediates and from side reactions. Although the carcinogenicity of D&C Orange No. 17 was revealed by an animal bioassay, the bioassay did not establish whether the carcinogenic response was produced by the principal color component or by one or more of its contaminants. It is theoretically possible that one of the contaminants could be responsible for the production of the carcinogenic response.

CTFA's assumption that the radiolabeled material was representative of the whole color additive (and, that, therefore, there is no need to be concerned with possible impurities) could not be substantiated. CTFA measured only the radioactivity of the substance that penetrated the skin and could not identify the components that actually penetrated the skin.

In addition, FDA's scientists could not determine from the data submitted by CTFA which constituents of the color additive penetrated skin, or whether impurities in the color additive would penetrate skin in the same manner as the primary color that was tested. It is possible (1) that the actual carcinogen could be a contaminant that penetrated the skin but was unlabeled and therefore undetected; (2) that virtually none of the principal color component penetrated the skin, and that the radioactive material found could be due to carcinogenic contaminants; and (3) that the degree of skin penetration by the actual carcinogenic agent is greater than that estimated by CTFA based on its assumption that the principal color component of D&C Orange No. 17 is the carcinogen.

CTFA's assumption that 100 percent of the carcinogenic agent is absorbed from the gastrointestinal tract was questioned by FDA's scientists because few chemicals are ever completely absorbed. There are many reasons for poor or limited absorption of chemical substances from the gastrointestinal tract, including (1) the instability of the chemical in acidic fluids, (2) enzymatic breakdown by digestive juices, (3) destruction by intestinal microorganisms, and (4) lack of lipid solubility.

FDA asked the panel to review CTFA's assumptions and the agency's concerns about impurities. The panel revised several of CTFA's assumptions and concluded that the agency's concerns regarding impurities, although important, could be addressed by making reasonable and appropriate assumptions about the possible effects impurities might have. The panel found it highly unlikely that impurities would significantly influence the risk assessment. The results of the panel's review are discussed in greater detail in a later section of this notice.

VII. CTFA's Assessment of Exposure to D&C Orange No. 17

In the report submitted to FDA on April 15, 1983, CTFA outlined the approach used in the CTFA risk assessments to estimate human exposure to D&C Orange No. 17. The cumulative amount of D&C Orange No. 17 absorbed by an individual was determined, based upon the products in which the color additive was used, the amount of each product used per application, the frequency of use of each product, the concentration of the color additive in each product, and the level of dermal absorption.

CTFA reported that by using both a prospective and a retrospective approach, it had determined the exposure to D&C Orange No. 17 through external cosmetic and drug product use. Data on the frequency of use of various external cosmetic and drug products came from two sources. The first is a 1-week prospective survey of female participants. The participants recorded the number of times in a week they used a range of cosmetic products including face powders and rouges, hair cosmetics, nail products, bathwater products, wash-off products, and various other externally applied cosmetic products. For products used less often than once per week, they were asked to report how often they generally used such products. The second source of data on frequency of use is from a retrospective survey of 1,129 customers of a chain of stores run by a major cosmetic manufacturer. Because the individuals in this survey were customers of specialty cosmetic stores, they are likely to have above-average usage patterns. For both sets of data, for each product, CTFA listed an average and an upper 90th percentile value of frequency of usage.

Data on the amount of each product per application were provided from the responses to a survey of CTFA member companies to obtain the results of existing studies on this subject. The values are the averages for each product as reported in CTFA's survey.

The April 15, 1983, report presented data derived from the skin absorption study conducted by Dr. Thomas J. Franz on the proportion of the D&C Orange No. 17 contained in each product that is likely to be absorbed. The skin

absorption study conducted by Dr. Franz is described in detail in a separate report (Ref. 9). Briefly, the absorption of ^{14}C-labelled D&C Orange No. 17 through half-thickness human abdominal skin was studied using Franz diffusion cells. Absorption under each of four experimental conditions described in the study was tested on duplicate sections of skin from each of three donors. The receptor phase (isotonic saline, pH 7.6, 37 °C) was sampled for radioactivity and replaced by fresh saline at 4, 8, and 12 hours, and at 12-hour intervals until four steady-state readings were obtained, or 72 hours after application of the color additive. The daily absorption rates and the percentage of the applied color additive absorbed over 3 days were calculated.

CTFA believes that the amount of D&C Orange No. 17 applied per square centimeter in these experiments was similar to or greater than the corresponding amount that would be applied in externally applied cosmetics and drugs. Hence, it concluded that the experimental permeability data are likely to be reasonably applicable to absorption of the color additive from a cosmetic or drug applied to the skin.

CTFA provided estimates of the amount of the color additive absorbed daily by combining the information on daily usage (upper 90th percentile) of the external cosmetic and drug products with data on the D&C Orange No. 17 content of the products (average and maximum) and estimates of the proportion of the color additive absorbed. CTFA emphasized that these data were deliberately chosen to overestimate exposure.

The usage values are upper 90th percentile values. The concentration of D&C Orange No. 17 is presented both as the maximum used in any formulation of each product type and as the average concentration in formulations that contain D&C Orange No. 17. For all product categories, there are many formulations that do not contain D&C Orange No. 17. Thus, a true "average" would be much lower, and the "average" values listed greatly overestimate the extent of exposure to D&C Orange No. 17 from its use in externally applied cosmetic and drug products.

By summing the values of D&C Orange No. 17 absorbed per day for each product containing the color additive, CTFA determined the "worst case" maximum amount absorbed for all or any combination of products. Summing all values gives a daily "worst case" absorption of 0.015 to 0.021 microgram or 0.00029 to 0.00039 microgram per kilogram per day for a 53 kilogram adult female using all products containing the maximum level of D&C Orange No. 17 at the upper 90th percentile usage frequency.

The panel, at FDA's request, critically evaluated CTFA's assessments and the underlying assumptions. A discussion of the panel's evaluation is provided in a later section of this notice.

VIII. CTFA's Low-Dose Carcinogenic Risk Assessment Approach

CTFA calculated both the "best conservative estimate" and the "upper bound estimates" of risk from the use of D&C Orange No. 17 in externally applied cosmetics and drugs, using currently accepted methods of risk assessment. The low-dose risk assessment proceeds in four steps:

1. Selection of the set of data on tumor incidence judged most appropriate as the basis for inference of human risk;
2. Extrapolation of these data to provide "best estimate" calculations, thus providing a range of risk to mice and rats at low-dose levels;
3. Extrapolation of the potential risk to humans at low-dose levels; and
4. Calculation of the potential risk to humans at the likely level of exposure from known patterns of use.

CTFA acknowledged that each of these steps required the use of assumptions with varying degrees of certainty. It was standard procedure by CTFA to make highly conservative "worst case" assumptions at each step, so that the final estimates likely overstated the actual risks by large factors. In its report, CTFA presented both "best conservative estimate" and "upper bound estimate" calculations to illustrate the range of potential risk. The "best conservative estimate" was based upon the extrapolation curve that best fits the experimental data, but also included such highly conservative "worst case" elements as the assumption that an individual consumer will be in the upper 90th percentile for frequency of use of all cosmetic products and will use only those cosmetic products that contain D&C Orange No. 17 at the maximum concentration. The "upper bound estimate" includes all "worst case" assumptions.

The CTFA risk assessment combined adenomas and carcinomas from the mouse liver tumor data and used the "worst case" maximum projections of human exposure and skin penetration. The multistage extrapolation model using the "worst case" maximum human exposure provides a "best conservative estimate" of potential lifetime risk to humans of 4×10^{-11} (1 in 25 billion), and an "upper bound estimate" of 7×10^{-11} (1 in 14 billion).

For the rat liver tumors, CTFA again combined both adenomas and carcinomas in order to provide a very conservative "worst case" estimate of potential risk to humans. The multistage extrapolation model using the "worst case" maximum human exposure provided a "best conservative estimate" of potential lifetime risk to humans of 1.1×10^{-19} (1 in 10 sextillion), and an "upper bound estimate" of 2.1×10^{-10} (1 in 4.8 billion).

IX. Review of D&C Orange No. 17 by the Scientific Review Panel

FDA's evaluation of the petitions for permanent listing of these color additives, and other available information, raised questions concerning whether CTFA's risk assessment was valid. As discussed above, FDA convened the panel to address these questions. The membership of the panel is outlined in the Federal Register of June 26, 1985 (50 FR 26379), which is incorporated by reference.

The panel was charged to evaluate the available data, information, and views on the color additives and to provide answers to the following questions:

1. Can valid quantitative risk assessments be performed for these color additives?
2. Does the available information support the data analysis and risk assessments that have been performed and are before the agency?

X. Report of the Color Additives Scientific Review Panel

The panel evaluated the possibility of performing a scientifically valid carcinogenic risk assessment on D&C Orange No. 17 for externally applied drug and cosmetic uses. The panel did not consider risk assessments for other toxic endpoints—indeed, it was not necessary to do so because no safety concerns other than carcinogenicity have been associated with the external uses of D&C Orange No. 17. The panel's report contains a discussion on the assumptions that must be made in conducting a risk assessment and the uncertainties that are associated with such assumptions. The report is supported by several recent government agency efforts directed at developing a consensus of risk assessment: (1) The National Academy f Sciences Report on Risk Assessment; (2) The Office of Science and Technology Policy Document on Chemical Carcinogenesis; and (3) The Executive Committee, Coordinating Committee on

Environmental and Related Programs Report on Risk Assessment.

The report contains a scientific introduction section for the major topics being discussed as well as a section on the general assumptions used in risk assessment of colors. The report discusses the risk assessments for each of the color additives by discussing major topics for each and the color additive-specific assumptions used, with the focus on the risk under practical conditions of use. Each chapter also contains a risk characterization section which discusses the risk assessment of the individual color additive.

In its report, the panel critically reviewed the risk assessments submitted by CTFA. This included a detailed examination of the risk assessment methodology used by CTFA. In a summary chapter of the report (Chapter 9) the Panel stated that:

> In order to obtain a better perspective on the very complex and multifaceted problem of assessing exposure and toxic effect of the dyes, it was imperative to search for the many obvious or hidden, explicitly stated or implied assumptions associated with risk assessment of the dyes. In dissecting the presented problem into the smallest possible components, for which separate solutions might be formed, the Panel opted for starting with formulating the assumptions according to CTFA's line of reasoning (it should be emphasized, however, that CTFA made these assumptions to, presumably, derive a conservative risk estimate, while not necessarily supporting them). This was followed by a careful analysis of the validity of the statements, the possible alternatives to dealing with the gaps in knowledge and lack of information, and the quantitative assessment of the impact of the assumption on the magnitude of the risk of cancer, assuming that the dyes do pose such a risk to humans.
>
> While evaluating the many kinds of uncertainties in hazard identification, exposure assessment, and dose-response assessment, the Panel developed the view that, rather than limiting its role to analyzing CTFA's lines of reasoning, it attempt to use its analysis to generate modified risk estimates. This includes an estimate of the absorbed dose based on more "reasonable" assumptions than those used in the CTFA assessments.

In the risk characterization section in the various dye chapters in the report, the panel compared the 90th percentile and the average usage (based on reasonable estimates). For the purpose of presenting the panel's assessment of the numerous assumptions used in the CTFA risk assessments, the agency has summarized that portion of the panel's report which discusses the assumptions and the associated uncertainties. The summary below deals with assumptions which are relevant to all color additives reviewed by the panel.

A. The Panel's Assumptions Used in Hazard Identification

The panel generally accepted the assumptions used in the CTFA risk assessments largely because there seem to be no alternatives with higher degree of validity for the uncertainties involved and because they are consistent with what the panel understood FDA's policy to be. The panel believed the assumptions it relied upon to be conservative, i.e., are more likely to overestimate rather than underestimate the true risk.

The panel's assumptions concerning hazard identification were:

1. Because all six dyes of concern are animal carcinogens in some assay, they are suspect human carcinogens. (The panel made no evaluation of the weight-of-evidence for human carcinogenicity from the animal test results.)

2. Orally administered or ingested dyes are equally well absorbed in animals and humans, regardless of the test concentration of the dye and of the vehicle used.

3. Studies involving high doses of a compound under test are appropriate for low-dose extrapolation.

B. The Panel's Assumptions Used in Exposure Assessment

The panel's general assumptions regarding exposure assessments were:

1. The dyes are equally absorbed in rodents and man.

2. Dyes which penetrate the skin are as effective in evoking a carcinogenic response as if ingested.

3. For each dye, exposure is for 60 years (in contrast to CTFA's use of 70 years) and risk is not influenced by age at exposure. This results in a correction factor of 6/7.

4. An arbitrary value should be used to reflect the fact that cosmetic products contain other dyes than those of concern (or no dyes at all). Compared to the CTFA estimate, this results in a correction factor of 0.5.

5. Based on data for D&C Red No. 19 only, the average concentration of all dyes in commercial products is 25 percent of the highest concentration allowed. Compared to the CTFA estimate, this results in a correction factor of 0.25.

6. The skin model used for the skin absorption studies is appropriate for assessing the exposure to absorbed dye. Although the model is likely to overestimate the risk for products applied to the facial skin (skin penetration rates are likely to vary for different areas of the body), the model may underestimate the real absorption rate by a factor of 3.

7. In interpreting the results of the in vitro study on the absorption rates over time, the true absorption rate equals the steady state rate. Where the test did not reveal a steady state, twice the maximum rate at the end of 3 days approximates the true absorption rate.

8. Both types of CTFA surveys of the frequency of the use of dye containing products overestimate the frequency among the general population.

9. The absorbed amount of dye per day can be estimated by multiplying the amount of dye per day available for absorption by an absorption rate constant, as estimated from the in vitro tests. There is insufficient information, however, to calculate a better, less conservative estimate.

10. For each dye, the total exposure is the sum of exposures to all products containing the same dye.

11. The amount of dye-containing product per application is approximately 5 to 10 milligrams per square centimeter.

12. With the exception of nail products, the composition of the vehicle used in the commercial products does not affect the absorption rate assessed with the in vitro skin model. There is insufficient information to generate a best estimate of the absorption rate for each kind of commercial vehicle.

13. In an appropriate vehicle, there is no difference in absorption rate between a primary dye and its lake.

14. Based upon consideration of the structure and toxicity of actual impurities found in certified lots, the skin penetrance rates of subsidiary colors are not likely to be significantly different from that of the principal constituent. The skin penetrance rates of the other substances of concern (e.g., residual starting materials) have, at most, an effect of multiplying the risk by 1.2. This results in a correction of CTFA's estimate of the exposure by a factor of 1.2.

The panel's product-specific assumptions regarding exposure assessments were:

1. The absorption rate for hair cosmetics is 1.2 percent of the applied amount. This results in a correction of CTFA's estimate by a factor of 0.6.

2. No absorption occurs from dyes in nail products (CTFA assumed that 1 percent of the applied amount will penetrate the skin).

3. For bathwater products, 2 percent of the applied amount reaches the skin.

4. For wash-off products (including bathwater products), there is an absorption of 25 percent (CTFA assumed an absorption of 50 percent and excluded bathwater products from this consideration). This results in a

correction of CTFA's estimate by a factor of 2.

5. For products other than wash-off products, there is an absorption of 50 percent (CTFA assumed an absorption of 100 percent). This results in a correction of CTFA's estimate by a factor of 2.

C. The Panel's Assumptions Used in Dose-Response Assessment

1. In test animals, 50 percent of orally administered dyes are absorbed from oral studies and the carcinogenic response is caused by this absorbed portion. This results in a correction of CTFA's estimate by a factor of 2.

2. On a milligram per kilogram body weight basis, dose levels used in animal tests have the same quantitative effect on the cancer incidence in humans. There is insufficient information for assessing the best estimate of the correct dose unit for use in extrapolating animal risk to human risk of cancer.

3. The average body weight for an adult woman is 53 kilograms.

4. The linearized multistage model reflects the true relationship between dose and response. The linearized multistage model may offer no added protection, however, in the convex portion of the dose-response curve. Low-dose linearity may overestimate the risk by several orders of magnitude if low-dose linearity is not present.

5. The most sensitive animal tumor data should be used to extrapolate risk from animal data to humans.

D. The Impact of the Panel's Assumptions on CTFA's Risk Estimate

In the chapters of the report concerning specific dyes, the panel applied the foregoing product- and dye-specific assumptions and correction factors to the usage data contained in the CTFA risk assessments. The panel also applied these assumptions to the survey estimates of 90th percentile exposure (the Risk/90 values) and average and "reasonable" estimates of exposure (Risk/Rea), thereby deriving revised risk estimates.

The impact on CTFA's risk assessment of the panel's general, quantifiable assumptions concerning exposure and dose-response are:

1. For skin absorption, a correction factor of 0.8 times the CTFA estimate (6/7×0.5×0.25×3×1.2×2).

2. For incidental ingestion of lip products, a correction factor of 6/7 times the CTFA estimate (a number of factors relevant only to skin absorption or not relevant to lipstick products do not apply).

3. At low dose levels, the risk of cancer, as computed with the linearized multistage risk model, is directly proportional to the dose levels.

The panel concluded that the correction factor of 0.8 for skin absorption is inconsequential when compared to the uncertainties in the assumptions that are difficult to quantify. The panel cautioned that the correction factor for skin absorption does not mean that the risk estimate is precise within 20 percent of the actual human risk. On the contrary, the figure merely represents the fact that, for the various quantifiable assumptions, underestimations and overestimations of risk in the CTFA estimates basically cancel out.

The panel also noted that many of the assumptions are not quantifiable. The panel, following prudent public health policy, stated that it accepted assumptions which are likely to overestimate rather than underestimate risk in the cases difficult to quantify and is of the opinion that the human risk in the risk estimates it made is more likely to be over- rather than under-estimated.

E. Specific Assumptions

The panel in its review of risk assessment for D&C Orange No. 17 evaluated a number of CTFA's specific assumptions relevant to the color. The assumptions and the panel's comments are as follows:

1. CTFA assumed that for creams and oils the absorption rate is 0.01 percent per day.

The panel stated that the skin test revealed rates of 0.003 to 0.007 percent of the applied amount per 24 hours, implying an overestimation of the absorption by a factor of 2. The panel recognized that the real factor is unknown because it is not clear whether the rates refer to a maximum rate or a steady state rate.

2. CTFA assumed that the absorption rate for D&C Orange No. 17 in talc is 0.001 percent per day of the amount applied.

The panel stated that CTFA mentioned 0.001 percent absorption in its text, but printed 0.00009 percent in Table 6, which referenced Table 2 in Franz's report. The latter uses the value 0.001 percent. The panel used 0.001 percent.

3. CTFA assumed that the use of Volpo 20 in the receptor of the Franz cell will not significantly alter the skin penetration.

Based on its review of these color specific assumptions, the panel utilized the following assumptions in risk characterization:

(a) For creams and oils, the skin absorption rate is 0.005 percent per day of the amount applied, which is half the rate assumed by CTFA.

(b) For talc formulations, the skin absorption rate is 0.001 percent per day of the amount applied. This is in agreement with the rate assumed by CTFA.

(c) The low skin absorption rate of D&C Orange No. 17 is unlikely to be caused by the insolubility of the dye in the receptor phase. Replacing the usual saline receptor phase by one containing Volpo 20 did not result in increased dye penetration.

The panel also utilized the following product specific assumptions in risk characterization:

(a) For nail products, the absorption of dyes is assumed to be zero, as compared to CTFA's assumption that no dye will be absorbed through the nail but that during application 1 percent of the dye may reach the skin or cuticle, where it will be available for absorption at the usual 1 percent rate.

(b) For products other than "wash-off" products, it is assumed that not more than 50 percent of the amount applied will stay available for absorption. CTFA assumed that the applied amount equaled the available amount.

F. The Panel's Interpretation of the Long-Term Studies

Prior to revising CTFA's risk estimates, the panel evaluated the available long-term studies of D&C Orange No. 17 in laboratory animals. The panel agreed with FDA that the 1.0 percent dosage level of D&C Orange No. 17 feeding study in rats was adequate and well-controlled and resulted in a statistically significant increase in the incidence of liver tumors (hepatocellular adenoma and carcinoma) in female rats as compared to controls.

In the case of D&C Orange No. 17, as with all the color additives it reviewed, the panel did not evaluate the weight-of-evidence for carcinogenicity to humans. Rather, the panel accepted as FDA's policy that any chemical shown to induce cancer even in only one strain, gender, and species, at one dose in one experiment, is an animal carcinogen. In light of the fact that D&C Orange No. 17 is an animal carcinogen by FDA's standards, the panel considered that there was an appropriate empirical basis for estimating the possible cancer risks to man presented by the external uses of D&C Orange No. 17.

The panel reached this conclusion even though in its view the information from the D&C Orange No. 17 feeding study in mice does not provide definitive evidence that the additive is a carcinogen in mice. The panel found the

mouse study to be well-controlled but considered the observed increase in liver tumors in the high-dose male mice to be equivocal. Nevertheless, the panel did prepare revised risk estimates based on the data from the mouse study.

G. Revised Risk Estimates

The panel's final step in evaluating the adequacy of CTFA's risk estimates on the external uses of D&C Orange No. 17 was to determine the total amount of the dye absorbed per day. In light of the fact that CTFA's information on the usage frequency that indicated that D&C Orange No. 17 was present in four different groups of products, the panel calculated that amount to be:

0.00189 microgram per day as an average of the prospective survey;

0.00635 microgram per day as the upper 90th percentile of the prospective survey;

0.00367 microgram per day as an average of the retrospective survey; and

0.007 microgram per day as the upper 90th percentile of the retrospective survey.

The comparable amounts calculated according to the CTFA assumptions are the upper 90th percentiles 0.0208 microgram per day (prospective survey) and 0.01542 microgram per day (retrospective survey). The panel believed that the prospective survey yielded less biased usage frequencies. Calculation of the resulting cancer risk estimates was, therefore, based on dose estimates based on the survey. At these very low dose levels, the dose-response curve is linear, meaning that the risk is directly proportional to the dose. The panel's revised estimates are based on 53 kilograms as a lifetime weight average for women, and include the panel's general correction factor of 0.8.

The panel's revised risk estimates are as follows:

	Risk (CTFA/90)*	Risk/90	Risk/Rea
Rat	2.1×10^{-10}	9.1×10^{-11}	1.5×10^{-11}
Mouse	0.7×10^{-10}	1.7×10^{-11}	0.5×10^{-11}

*Note that CTFA does not give an average exposure esimate for D&C Orange No. 17.

Risk(CTFA/90) is the CTFA risk estimate at the upper 90th percentile of exposure.

Risk/90 is the risk estimate based on the panel's calculation at the 90th percentile of exposure.

Risk(REA) is the risk estimate based on the panel's calculation of a more reasonable estimate of exposure.

The above risk estimates are based on the reasonable estimates of exposure, whenever the panel believed that it was possible to make such an estimate. In situations where available data would allow for a choice between "degrees of reasonable estimate," the panel consistently selected the estimate associated with the higher risk.

H. The Panel's Conclusion

The panel concluded that the animal studies were properly controlled except for a lack of data on the purity of the pigment (subsidiary color) or on the levels of impurities, at least one (2,4-dinitrobenzeneamine) of which is a strong mutagen. In response to the agency's concerns regarding whether the available data and information adequately characterized the risk presented by exposure to possible impurities, the panel concluded that the level of impurities may have an impact on risk assessment only if the degree of potency of the impurities is greater, by several orders of magnitude, than the degree of potency of the pigment. Based on the strong mutagenicity of D&C Orange No. 17 without activation in several strains, the mutagenicity of the azo reduction product, and the reported mutagenicity of 2,4-dinitrobenzeneamine with or without activation, the panel concluded that it is unlikely that the carcinogenic "potency" differs from the parent compound by several orders of magnitude, and the general assumption concerning the likelihood that impurities would have no effect on the risk assessment is even more likely for this color additive.

XI. FDA's Decision to Permanently List D&C Orange No. 17

A. Reliance on Risk Estimation Techniques

The data and information regarding the safety of D&C Orange No. 17 support FDA's conclusion that the substance induces cancer when tested in laboratory animals. The data and information, however, do not support any other finding of toxicity.

In the past, because the data and information show that D&C Orange No. 17 is a carcinogen when ingested by laboratory animals, FDA in all likelihood would have terminated the provisional listing and denied CTFA's petition for the externally applied uses of D&C Orange No. 17 without any further discussion. In the present instance, however, CTFA has presented arguments that this color additive can be regulated for safe use in externally applied drugs and cosmetics. The arguments CTFA has presented are based on the premise that a determination of safety may be based on risk assessment techniques. FDA agrees that risk estimation methods are frequently helpful in evaluating the safety of carcinogenic substances. It was for these reasons that the agency requested the panel to determine whether the data and information available concerning D&C Orange No. 17 provided an adequate basis from which to make reliable risk estimations.

FDA agrees with the panel that CTFA's risk estimates on the use of D&C Orange No. 17 in externally applied drugs and cosmetics, as modified in the panel's report, represent a reliable upper bound risk and that those risk estimates can be used to evaluate the proposed external uses of D&C Orange No. 17. FDA also agrees, for the purpose of conducting a risk assessment, with the panel's resolution of the agency's concerns regarding the possible toxicity of impurities in the color additive.

B. The Safety of D&C Orange No. 17

Under section 706(b)(4) of the act (21 U.S.C. 376(b)(4)), the so-called general safety clause of the statute, FDA cannot approve a color additive for a particular use unless the data presented to FDA establish that the color additive is safe for that use. Although what is meant by safe is not explained in the general safety provision, the legislative history of the act makes clear that safety requires proof to a reasonable certainty that no harm will result from the proposed use of an additive. Because FDA considers D&C Orange No. 17 to be a carcinogen when ingested by laboratory animals, as discussed above, the Delaney Clause (section 706(b)(5)(B)(i) of the act) is applicable. A strictly literal application of the Delaney Clause would prohibit FDA from finding that D&C Orange No. 17 is safe and, therefore, prohibit FDA from permanently listing the color for externally applied uses in drugs and cosmetics. However, as seen from CTFA's and the panel's risk estimates, the calculated risk for these uses of D&C Orange No. 17 is extremely low. In fact, the level is three to four orders of magnitude lower than that level of risk which the agency accepts in other areas concerning carcinogens; for example, its procedures and criteria for permitting carcinogenic food additive residues in animal tissues under section 512(d)(1)(H) of the act, the DES proviso to the Delaney Clause (21 U.S.C. 360b(d)(1)(H)) (see 50 FR 45530, 45541; October 31, 1985; FDA refers to these procedures and criteria as the sensitivity of the method or SOM procedures). With such a negligible risk, there is no gain to the public and the statutory purpose is not implemented or served by an agency action delisting the substance.

Under these circumstances, FDA concludes that it should not interpret the Delaney Clause to require a ban on this use of D&C Orange No. 17. Therefore, FDA has decided to exercise its inherent authority under the *de minimis* doctrine

and concludes that the Delaney Clause does not require a ban in the case of the externally applied uses of D&C Orange No. 17. Because there are no other safety problems with this use of D&C Orange No. 17, FDA finds that the externally applied uses are safe.

C. CTFA's Legal Arguments

In its April 15, 1983, submission, CTFA argued that the applicable statutory authority under the act and judicial precedent authorize FDA to apply a *de minimis* interpretation of the Delaney Clause for a carcinogenic color additive that presents an insignificant risk of cancer. CTFA also argued that the Delaney Clause does not apply to the external uses of D&C Orange No. 17 because the tests on D&C Orange No. 17 are not appropriate for the evaluation of the substance.

FDA agrees with the former position and in the following section of this notice discusses the applicability of the *de minimis* doctrine to D&C Orange No. 17. The agency, however, disagrees with CTFA's latter argument, one that draws heavily on the agency's decision to list the color additive lead acetate (45 FR 72112, October 31, 1980; 46 FR 15500, March 6, 1981). CTFA's studies show that a portion of the radiolabeled material in the D&C Orange No. 17 used for percutaneous study penetrated the skin and entered the circulatory system. Under these circumstances, in the absence of any metabolic or other data suggesting that ingestion studies are inapplicable, ingestion studies are appropriate as a basis for risk assessment of the external uses of D&C Orange No. 17.

Moreover, FDA's decision concerning lead acetate was based upon the unusual combination of scientific facts, peculiar to the use of lead acetate in hair dyes, which the agency recognized "will rarely, if ever, be presented again in this context" (45 FR 72112, 72115; October 31, 1980). Similar facts do not exist in the case of D&C Orange No. 17. For example, a key factor that influenced FDA's judgment that the Delaney Clause just did not apply to lead acetate was the fact that a background level of lead is always present in the blood of humans, a background level much greater than the possible increase in lead burden that would result from the use of lead acetate in hair dyes. There is, of course, no background level of D&C Orange No. 17 in humans. The agency believes that the tests on D&C Orange No. 17 are appropriate for an evaluation of the substance under the Delaney Clause.

D. The de Minimis Doctrine and Its Applicability to D&C Orange No. 17

Two conditions must apply to justify an agency's exercise of its authority to interpret a legal requirement as not requiring action in *de minimis* situations. First, it must be consistent with the legislative design for the agency to find that a situation is trivial and, therefore, one that need not be regulated. *Alabama Power Co.* v. *Costle*, 636 F.2d 333, 360 (DC Cir. 1979). Second, it must be clear that the situation is in fact trivial, and that no real benefit will flow from regulating the particular situation. *Environmental Defense Fund* v. *Environmental Protection Agency*, 636 F.2d 1267, 1283–1284 (DC Cir. 1980). Both conditions apply here.

1. The establishment of a *de minimis* exception to the Delaney Clause is consistent with the legislative design.

In *Alabama Power Co.* v. *Costle*, supra, the court stated that the implication of *de minimis* authority is consistent with most statutes. The court stated that unless Congress has been extraordinarily rigid, there is likely a basis for an implication of such authority. *Id.* at 360–361. That Congress was not so rigid as to preclude the implication of *de minimis* authority under the Delaney Clause is evidenced both by the stated congressional intent in enacting the Delaney Clause and by the stated purpose of this provision.

The clearest statement of the congressional intent for the Delaney Clause is in the legislative history of the Color Additive Amendments of 1960. The Senate considered that the calculation of risk would permit interpretation of the Delaney Clause to allow color additives producing a negligible risk. This is clear from a colloquy on the Senate floor initiated by Senator Jacob Javits in debate on his motion to reconsider the vote to approve the Color Additive Amendments. Senator Javits, focusing on the Delaney Clause, made the record clear in discussion with Republican leader Senator Dirksen and committee chairman Senator Hill that the Senate had agreed to pass the Color Additive Amendments with the Delaney Clause based upon its understanding that the authority conferred by that clause "should be used and applied within the 'rule of reason.'" 106 Congressional Record 15381 (July 1, 1960).[1] Both Senator Dirksen and Senator Hill agree that the "rule of reason" was to be applied in interpreting the Delaney Clause. *Id.* On that basis, Senator Javits did not pursue his motion to reconsider.

The term "rule of reason" was taken from a report to the President from the President's Science Advisory Committee and from the Departments of Agriculture and of Health, Education, and Welfare (the predecessor to the Department of Health and Human Services) that analyzed the effect of the Delaney Clause that is applicable to food additives. That report defines the "rule of reason" as meaning that: "Every statute must be interpreted in the light of reason and common understanding to reach the results intended by the legislature." 106 Congressional Record 15380. The report stated its conclusion that "an area of administrative discretion based on the rule of reason is unavoidable if the clause is to be workable." 106 Congressional Record 15381.

This report on implementation of the food-additive provision, relied upon by the Senators as illustrating their understanding of the types of circumstances in which the "rule of reason" would appropriately be applied, accurately predicted the advent of the science of risk assessment. The report stated that: "From the experience obtained in animal experiments and study of humans who have been exposed to carcinogens in the course of their work the panel believes that the probability of cancer induction from a particular carcinogen in minute doses may be eventually assessed by weighing scientific evidence as it becomes available." 106 Congressional Record 15380–15381.

Thus, the Senate agreed to adopt the color additive Delaney Clause only with the understanding that the clause would be administered with "a rule of reason," premised on the expectation that scientists would be able to determine the "probability of cancer induction." Thus, far from having been "extraordinarily rigid," Congress clearly contemplated that those administering the Delaney Clause would have discretion to implement that provision in a reasonable way.[2]

[1] More recently, Senator Javits reviewed this discussion. On July 10, 1985, he sent Margaret Heckler, Secretary of the Department of Health and Human Services, a letter stating that his views had not changed since 1960. He stated that it was his continuing understanding that the rule of reason "would dictate that where the danger to the public is negligible in using products with such color additives, then use should not be prohibited." A copy of Senator Javits' letter to Secretary Heckler is included in the record of this rulemaking.

[2] This grant of discretion is not inconsistent with the fact that Congress clearly intended to prevent the imposition of a tolerance for a carcinogen. Where the probability of harm is so small as to be of no practical significance, it is reasonable and

Continued

The purpose of the Delaney Clause in section 706 of the act is, after all, to protect the public from the possibility of increasing cancer risks through the use of color additives. It does not advance this purpose to prohibit uses that present a risk that is, for all practical purposes, zero. Congress recognized this fact in warning FDA not to "go overboard" in applying the Delaney Clause. 106 Congressional Record 15381. Thus, it is not inconsistent with the Delaney Clause to permit some uses of a carcinogenic color additive when those uses are shown to present a potential carcinogenic risk that is so trivial, based on extremely conservative statistical analyses, as to be the functional equivalent of no risk at all.

This interpretation of the Delaney Clause finds support in recent case law. In *Monsanto* v. *Kennedy*, 613 F.2d 947 (DC Cir. 1979), the court held that not all chemicals that become components of food need be considered food additives. The court stated that FDA has the authority to ignore a chemical that migrates from plastic packaging material into beverages if the amount of the chemical that migrates is *de minimis*. The court made that statement after it had found that some amount of the chemical in question would become a component of food by migration from packaging material—thus undeniably satisfying a literal reading of the statute. The court was concerned that the Commissioner may have reached his determination in the belief "that he was constrained to apply the strictly literal terms of the statute irrespective of the public health and safety considerations." 613 F.2d at 954. Accordingly, the court emphasized that there is "latitude inherent in the statutory scheme to avoid literal application of the statutory definition of 'food additive' in those *de minimis* situations that, in the informed judgment of the Commissioner, clearly present no public health or safety concerns." *Id.* Thus, the *Monsanto* decision is important to the agency's present action even though that case involved the definition of "food additive" and not the application of the Delaney Clause, and even though FDA, when it issued the order that was ultimately reviewed by the court, had not made a final determination as to the carcinogenicity of the chemical at issue, acrylonitrile monomer.

The court also held in *Monsanto* that the *"de minimis"* concept, applied to the threshold "food additive" definition, could be utilized to allow the marketing of a substance that presents no real public health risk. See 613 F.2d at 955–956. Thus, the court's decision in *Monsanto* has the practical effect of shielding substances that present effectively no carcinogenic risk from the Delaney Clause. Although the court did not explicitly interpret the Delaney Clause as inapplicable to such substances, the court presumably knew that if a carcinogenic chemical was disregarded as *de minimis* in relation to the food additive definition, the chemical would not be subject to the Delaney Clause, which applies only when that definition is met. Necessarily, therefore, the court regarded this consequence as legally warranted.

Moreover, in *Scott* v. *FDA*, 726 F.2d 322, 325 (6th Cir. 1984), the Sixth Circuit upheld the so-called constituents policy, whereby FDA may approve known carcinogens present in color additives as intermediaries or impurities present at levels too low to cause a response using conventional tests. Noting that FDA had determined the public health risk presented by D&C Green No. 5 was negligible, the court reasoned:

> • • • We find this determination by the *Monsanto* court persuasive and relevant to the particular facts of the instant case. We agree with the FDA's conclusion that since it "has discretion to find that low level migration into food of substances in indirect additives is so insignificant as to present no public health or safety concern • • • it can make a similar finding regarding a carcinogenic constituent or impurity that is present in a color additive" 47 FR 24280 (1982).

In addition to the foregoing precedents, the state of scientific knowledge about cancer when the Delaney Clause was passed also supports the implication of *de minimis* authority under the Delaney Clause and the fact that the provision could not possibly have been meant to be "extraordinarily rigid." In 1958, there were only four substances that were known to induce cancer in humans: soot, radiation, tobacco smoke, and *beta*-naphthylamine (Ref. 13). Only 20 years later, scientists had identified 37 human carcinogens and over 500 animal carcinogens (Ref. 13). This growth in knowledge is in part the result of an enormous increase in carcinogenicity testing in laboratory animals. As testing increases, more and more substances are found to induce cancer at some site in at least some strain or sex of laboratory animal. For example, of the 86 compounds tested by the National Toxicology Program (NTP) and reported between July 1981 and July 1984, 50 percent were determined to induce some carcinogenic effect (Ref. 14). (It should be noted that many of the compounds tested by NTP were, prior to testing, suspected of being carcinogenic.) Furthermore, recent short- and long-term toxicity testing has shown that a large number of substances naturally present in food are mutagenic or carcinogenic (Ref. 15).

With the advent of sensitive chemical analytical methodologies, scientists have been able to find carcinogens throughout the food supply in extremely small quantities. In 1958, the available methodologies were far less sensitive than they are today. For example, as FDA stated in its 1979 SOM proposal, the sensitivity of the methodologies increased during the period between 1958 and 1978 by "between two and five orders of magnitude" (44 FR 17070, 17075; March 20, 1979). This improved sensitivity has allowed the detection of carcinogens in the parts per trillion level so that, as one scientist has reported, "today substances can be routinely measured at concentrations up to a million times less than was possible in 1958" (Ref. 13).

There is no indication that in 1958 Congress foresaw the likelihood that, within less than 30 years after the Delaney Clause was enacted, science would have progressed so far as to be able to document the widespread presence of trace amounts of proven carcinogens in food. There is no indication that Congress anticipated the extent to which substances, then regarded either as absent from foods or as noncarcinogenic on the basis of less adequate technology, would later prove to be carcinogenic. In short, the scientific knowledge about carcinogens was much more limited in 1958 than it is today. The solution Congress decided upon in 1958 for handling added carcinogens, given that state of knowledge, was not extraordinarily rigid but was entirely reasonable, i.e., a few substances, present at levels then detectable, would be banned; most food would be unaffected.

Under these circumstances, it would not be consistent with the legislative design for FDA, today, to attempt to prohibit all added carcinogens from the food supply provided the risks presented by permitted levels are trivial. Permitting merely a *de minimis* level of risk from such carcinogens is not only sound regulatory policy but is also consistent with the underlying purpose of the Delaney Clause as enacted in 1958—the assurance that the food supply will be free from any meaningful risk of cancer presented by substances added to food.

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appropriate to apply the *"de minimis"* concept. And, doing so does not in any way reflect an intent to set a tolerance.

For all the foregoing reasons, the agency concludes that it is consistent with the Delaney Clause to permit uses of a carcinogenic color additive when those uses are shown to present a carcinogenic risk that is so trivial, based on extremely conservative statistical analyses, as to be the functional equivalent of no risk at all.

2. The risk from the use of D&C Orange No. 17 in externally applied drugs and cosmetics is, in fact, so trivial as to be effectively no risk.

According to the panel's revised risk estimates, the highest lifetime level of risk presented by the external uses of D&C Orange No. 17 is 1 in 19 billion, i.e., 5.1×10^{-11}. This is not an actuarial risk. An actuarial risk is the risk determined by the actual incidence of an event. In contrast, the computed risk is a projection based on certain conservative assumptions that do not understate risk. The assumptions that were relied upon in this computation have been stated previously in the document based on the panel's computations. The risk from the use of D&C Orange No. 17 in externally applied drugs and cosmetics will not exceed 1 in 19 billion and is likely to be somewhere between that level and zero. The 1 in 19 billion level represents a 1 in 19 billion increase in risk over the normal risk of cancer in a lifetime—not annual—risk. FDA emphasizes that the 1 in 19 billion level of risk does not mean that 1 in every 19 billion people will contract cancer as a result. Rather, in all likelihood, no one will contract cancer as a result of this exposure.

In light of the level of risk presented by the external uses of D&C Orange No. 17, FDA finds that the uses are safe, that they impose no additional risk of cancer to the public, and that any risk they may present is of no public health consequence. It is in just these circumstances, where there is no meaningful increase in public health protection from applying the strict, literal terms of a legal standard, that the courts have found the *de minimis* doctrine to be applicable. For example, the court in *Monsanto* equated "*de minimis*" with a finding that migration of an indirect food additive is "insignificant" (613 F.2d at 947) in a context where the court clearly recognized that the real question was the toxicity of a particular level of migration.

Furthermore, FDA and other regulatory agencies have, in the past, found higher risks than those presented by D&C Orange No. 17 to be permissible. For example, in the ongoing SOM rulemaking proceeding, FDA has proposed that an assay method sufficient to detect a carcinogenic residue posing a calculated upper bound risk of 1 in 1 million is appropriate because such a level imposes no additional risk of cancer to the public (see 44 FR 17070, 17093; March 20, 1979). The agency has concluded that as a result of this use of the 1 in 1 million level of risk as far as can be determined in all probability, no one will contract cancer from admittedly carcinogenic residues in edible animal tissue. (See 50 FR 45530, 45541; October 31, 1985.)

In several proceedings involving the agency's policy for carcinogenic impurities in food and color additives, FDA has also found that a risk on the order of a 1 in 1 million lifetime risk is low enough to be considered safe within the meaning of the general safety clause. See, for example, the administrative record compiled in the rulemaking on D&C Green No. 6 (47 FR 14138; April 2, 1982).

Furthermore, in a notice published in the Federal Register of December 18, 1985 (50 FR 51551), the agency proposed that methylene chloride when used to decaffeinate coffee is safe, in light of the fact that the potential risk posed by permitted levels of methylene chloride residue in coffee does not exceed 1 in 1 million. In that notice, the agency also suggested that the lifetime risk for this use of methylene chloride to decaffeinate coffee is *de minimis*.

Other Federal agencies have also used a 1 in 1 million level as a basis for regulatory decisionmaking permitting human exposure to carcinogens (Ref. 16). In fact, they have sometimes made regulatory decisions that have allowed a cancer risk greater than 1 in 1 million. The Occupational Safety and Health Administration (OSHA), for example, has focused its regulatory efforts on risks in the workplace that are much higher than 1 in 1 million lifetime level of risk.

For example, under the Occupational Safety and Health Act (OSH Act) (29 U.S.C. 651 et seq.), OSHA issues health standards for the workplace. Before issuing a standard, OSHA must make a formal showing of "significant risk from exposure." Accordingly, OSHA uses quantitative risk assessment to compare the magnitude of risk presented by the various possible levels of exposure to a substance before establishing a permissible exposure limit. In the Federal Register of January 14, 1983 (48 FR 1864), OSHA established a new permissible exposure limit for inorganic arsenic after determining the risk of lung cancer death associated with such a level would be 8 cases per 1,000 workers exposed over a working lifetime. The standard was upheld by the Ninth Circuit Court of Appeals in *ASARCO* v. *OSHA*, 746 F.2d 483 (9th Cir. 1984). I similar action in the Federal Registe June 22, 1984 (49 FR 25734), OSHA published a final rule establishing a permissible exposure limit for ethyl oxide. The new 1 part per million permissible exposure limit represent risk of 12 to 23 excess deaths per 10, workers exposed over a working lifetime.

The Environmental Protection Age (EPA) in recent years has also relied upon the 1 in 1 million lifetime level reasonable criterion for separating h risk problems from low risk problem presented by the wide ranging environmental contaminants EPA m regulate. In the Federal Register of November 23, 1984 (49 FR 46294), EP proposed guidelines for carcinogen ri assessment. The proposal outlined a procedure for characterizing substan based on the experimental weight of evidence of carcinogenicity. For thos compounds classified as known or probable human carcinogens, EPA se the 1 in 1 million risk level as the "poi of departure" for determining what le of a carcinogen may cause concern.

For example, under the Safe Drinki Water Act (42 U.S.C. 300f et seq.), EP sets drinking water standards that contain maximum contaminant levels for toxicants, including carcinogens. Maximum contaminant levels for carcinogens that have been promulgat or proposed to date by EPA generally fall into lifetime risk ranges of 1 in 10,000 to 1 in 1 million (Ref. 17). Similarly, EPA recently proposed to establish the 1 in 1 million level as the "point of departure" in determining the level of control for all known and possible carcinogenic constituents compounds resulting from hazardous waste contamination (51 FR 1602, 1635; January 14, 1986). As an alternative, EPA proposed to consider estimates of population in determining the appropriate level of control for each constituent. Thus, if a very large numbe of people is believed to be potentially exposed to a very potent carcinogenic constituent released from contaminated land disposal units, EPA could decrease the level of risk to as low as 1 in 10 million. If the size of the potentially exposed populati n is not large, the "point of departure" would remain at the 1 in 1 million level. However, if a small number of people was believed to be exposed to the contaminant, such that the incidence of cancer would be expected to be small from the exposure, EPA would consider increasing the acceptable risk level to 1 in 100,000 or 1 in 10,000.

Although comparisons between the safety decisions made by OSHA and EPA with those made by FDA must be tempered by the fact that the decisions are made under different statutory frameworks, the decisions support the consensus proposition that a lifetime level of 1 in 1 million presents an extremely small risk.

Furthermore, FDA's conclusion that a 1 in 1 million lifetime level represents an insignificant level of risk has not been arrived at hastily. For example, when it first proposed the SOM procedures and criteria on July 19, 1973 (38 FR 19226), the agency stated that an acceptable level of risk for carcinogenic residues in edible animal tissues would be 1 in 100 million. In the Federal Register of February 22, 1977 (42 FR 10412), the agency concluded that the 1 in 100 million level was unnecessarily conservative in light of the numerous conservatisms implicit in risk assessment and because the level provided only a minor incremental increase in the degree of confidence presented by the higher 1 in 1 million level. The agency concluded that the 1 in 1 million level constituted a risk level that one could properly consider to present an insignificant public health concern (see also 44 FR 17070; March 20, 1979). In the most recent Federal Register document concerning the SOM rulemaking (50 FR 45530; October 31, 1985), the agency explained that it considered raising the level yet another order of magnitude to 1 in 100,000 but chose not to do so. FDA reasoned that in recent years the 1 in 1 million level has become a benchmark in the evaluation of the safety of carcinogenic compounds administered to food-producing animals.

Furthermore, the agency stated that there is currently widespread confidence that this level presents an insignificant risk of cancer. This point is underscored by the fact that every comment on the risk level aspect of the 1979 SOM proposal regarded the 1 in 1 million level as insignificant. In making the decision to retain the 1 in 1 million level for purposes of the SOM proceeding, FDA recognized explicitly that there may be a higher level of risk that is more appropriate to characterize as a "no residue" level, but that in light of the current uncertainties that accompany making a decision as to the most appropriate level of risk, the 1 in 1 million level was the most reasonable and defensible choice (50 FR 45542).

The level of risk presented by the external uses of D&C Orange No. 17 is extremely low. In relation to other risks regulated by FDA and other Federal agencies, the risk presented by the external uses of D&C Orange No. 17 is, indeed, trivial.

XII. Conclusion

Based on the foregoing, FDA concludes that the risk of cancer from the use of D&C Orange No. 17 in externally applied drugs and cosmetics is so low (1 in 19 billion) as to be effectively no risk, and that there would be no benefit to the public from prohibiting these uses of the color additive. Further, for the same reasons and because the available information indicates no other safety questions regarding the use of D&C Orange No. 17 in externally applied drugs and cosmetics, FDA concludes that the externally applied uses of D&C Orange No. 17 are safe. The agency is amending Part 74 to permanently list D&C Orange No. 17 for such uses.

The agency is describing the color additive in this regulation according to current Chemical Abstracts Service nomenclature, which differs somewhat from the nomenclature FDA previously used, and the agency is establishing new chemical specifications for the Part 74 listings that identify the color additive more precisely than those currently listed in 21 CFR 82.1267.

FDA is also modifying its regulations to conform them to the decisions announced in this document.

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that FDA considered and relied upon in reaching its decisions to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition (address above) by appointment with the information contact person listed above. As provided in § 71.15, the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

The agency has determined under 21 CFR 25.24(b)(3) (April 26, 1985; 50 FR 16636) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96-354) do not apply to actions of this type.

XIII. References

The following information has been placed on file at the Dockets Management Branch (address above) and is available for review in that office between 9 a.m. and 4 p.m., Monday through Friday. The final toxicity study reports, the agency's toxicology evaluations of these studies, and other information relied upon by the agency in reaching its decision are also on file at the Dockets Management Branch for public review.

1. Sontag, J.M., N.P. Page, and U. Saffiotti, "Guidelines for Carcinogen Bioassay in Small Rodents," DHEW Publication No. (NIH) 76-801, p. 14, 1976.

2. International Expert Advisory Committee to the Nutrition Foundation, "The Relevance of Mouse Liver Hepatoma to Human Carcinogenic Risk," September 1983.

3. "Interagency Regulatory Liaison Group (1979) Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks," *Journal of the National Cancer Institute*, 63:241-268, and Federal Register 44:131:39858-39879 (July 6, 1979).

4. Jackson, B.A., "Regulatory Interpretation of Proliferative Lesions of Rodent Liver," *FDA By-lines*, #1 (January 1981).

5. Bureau of Foods' Cancer Assessment Committee Reports on Benzidine and Aniline, December 20, 1983.

6. Klaassen, C.D., "Absorption, Distribution and Excretion of Toxicants," Chapter 3 *in* "Toxicology, The Basic Science of Poisons," Casarett, L.J. and J. Doull (Eds.), Macmillan Pub. Co. Inc., New York, pp. 26-44, 1975.

7. "Report of the Color Additive Scientific Review Panel," September 1985.

8. Memorandum to File from W. Gary Flamm, "Environ Report."

9. Franz, T.J., "Percutaneous Absorption of D&C Orange No. 17 Through Human Skin In Vitro," March 25, 1983.

10. Letter from J. Schwing to N. Estrin, October 19, 1977.

11. Cancer Assessment Committee Memorandum of Conference, August 5, 1982.

12. Cancer Assessment Committee Memorandum of Conference, January 20, 1983.

13. Wilson, R., "Risks Caused By Low Levels of Pollution," *Yale Journal of Biology and Medicine*, 51:37, 48, 1978.

14. Haseman, J., et al., "Results From 86 Two-Year Carcinogenicity Studies Conducted by the National Toxicology Program," *Journal of Toxicology and Environmental Health*, 14:621, 634, 1984.

15. Ames, B., "Dietary Carcinogens and Anticarcinogens," *Science*, 221:1256, September 23, 1983.

16. Milvy, P., "A General Guideline for Management of Risk from Carcinogens," *Risk Analysis*, 6:69, 1986.

17. Crouch, E., et al., "The Risks of Drinking Water," *Water Resources Research*, 19 1359, 1983.

XIV. Objections

Any person who will be adversely affected by this regulation may at any time on or before September 8, 1986, file with the Dockets Management Branch (ADDRESS above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the

regulation to which objection is n and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. FDA will publish notice of the objections that the agency has received or lack thereof in the Federal Register.

List of Subjects

21 CFR Part 74

Color additives, Cosmetics, Drugs, Medical devices.

21 CFR Part 81

Color additives, Cosmetics, Drugs.

21 CFR Part 82

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Parts 74, 81, and 82 are amended as follows:

PART 74—LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

1. The authority citation for 21 CFR Part 74 is revised to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055–1056 as amended, 74 Stat. 399–407 as amended (21 U.S.C. 371, 376); 21 CFR 5.10.

2. By adding new § 74.1267 to read as follows:

§ 74.1267 D&C Orange No. 17.

(a) *Identity.* (1) The color additive D&C Orange No. 17 is 1-[(2,4-dinitrophenyl)azo]-2-naphthalenol (CAS Reg. No. 3468-63-1). The color additive is manufactured by diazotization of 2,4-dinitrobenzeneamine in acid medium and coupling with 2-naphthalenol in acid medium.

(2) Color additive mixtures for use in externally applied drugs made with D&C Orange No. 17 may contain only those diluents that are suitable and that are listed in Part 73 of this chapter for use in color additive mixtures for coloring externally applied drugs.

(b) *Specifications.* D&C Orange No. 17 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practice:

Volatile matter (at 135 °C), not more than 1.5 percent.

Matter insoluble in toluene, not more than 1.5 percent.

2,4-Dinitrobenzeneamine, not more than 0.2 percent.

2-Naphthalenol, not more than 1.2 percent.

4-[(2,4-Dinitrophenyl)azo]-1-naphthalenol, not more than 0.3 percent.

1-[(4-Nitrophenyl)azo]-2-naphthalenol, not more than 0.3 percent.

Lead (as Pb), not more than 20 parts per million.

Arsenic (as As), not more than 3 parts per million.

Mercury (as Hg), not more than 1 part per million.

Total color as determined by spectroscopy, not less than 95 percent.

(c) *Uses and restrictions.* The color additive D&C Orange No. 17 may be safely used for coloring externally applied drugs in amounts consistent with current good manufacturing practice.

(d) *Labeling.* The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(e) *Certification.* All batches of D&C Orange No. 17 shall be certified in accordance with regulations in Part 80 of this chapter.

3. By adding new § 74.2267 to read as follows:

§ 74.2267 D&C Orange No. 17.

(a) *Identity and specifications.* The color additive D&C Orange No. 17 shall conform in identity and specifications to the requirements of § 74.1267(a)(1) and (b).

(b) *Uses and restrictions.* The color additive D&C Orange No. 17 may be safely used for coloring externally applied cosmetics in amounts consistent with current good manufacturing practice.

(c) *Labeling.* The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(d) *Certification.* All batches of D&C Orange No. 17 shall be certified in accordance with regulations in Part 80 of this chapter.

PART 81—GENERAL SPECIFICATIONS AND GENERAL RESTRICTIONS FOR PROVISIONAL COLOR ADDITIVES FOR USE IN FOODS, DRUGS, AND COSMETICS

4. The authority citation for 21 CFR Part 81 continues to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055–1056 as amended, 74 Stat. 399–407 as amended (21 U.S.C. 371, 376); Title II, Pub. L. 86-618; sec. 203, 74 Stat. 404–407 (21 U.S.C. 376, note); 21 CFR 5.10.

§ 81.1 [Amended]

5. In § 81.1 *Provisional lists of color additives* by removing the entry for "D&C Orange No. 17" in paragraph (b).

§ 81.27 [Amended]

6. In § 81.27 *Conditions of provisional listing* by removing the entry for "D&C Orange No. 17" in paragraph (d).

PART 82—LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS

7. The authority citation for 21 CFR Part 82 is revised to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055–1056 as amended, 74 Stat. 399–407 as amended (21 U.S.C. 371, 376); 21 CFR 5.10.

8. By revising § 82.1267 to read as follows:

§ 82.1267 D&C Orange No. 17.

The color additive D&C Orange No. 17 shall conform in identity and specifications to the requirements of § 74.1267(a)(1) and (b) of this chapter.

Dated: July 28, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

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21 CFR Parts 74, 81, and 82

[Docket No. 83C-0129]

Listing of D&C Red No. 19 For Use in Externally Applied Drugs and Cosmetics

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is permanently listing D&C Red No. 19 as a color additive for use in externally applied drugs and cosmetics. FDA is taking this action because it has concluded that the