three sets of mice in the Gass study is appropriate (G–21). In order to make this determination, he carried out a Chi-squared test on each of the three data-sets (i.e., the results observed with each of the groups of mice tested). The Chi-squared statistic is based on the squared distances of the observed probit values from the fitted probit-log dose regression line. The calculated value is small if the observed probits do not deviate greatly from the fitted regression line; an absence of large deviation indicates with a high probability that the probit-log dose model is adequate.

Unlike the manufacturing parties' witnesses, who disregard the 6.25 and 12.5 ppb dosage levels in their computations, Dr. Condon used the data from all the dosage levels. He commented on his Chi-squared calculations as follows (G–21 at 2):

> The observed values do not differ significantly from those depicted by the fitted dose response curve at any of the doses used in this experiment. This means that none of the observed response values (mammary tumor incidence) should be dismissed as aberrant values.

If the probit-log dose model is accepted as correct, then there is no threshold level because this model presupposes that every dosage level induces a response.

Dr. Jerome Cornfield and Dr. Adrian Gross in effect incorporated in their testimony (G–25 at 2; G–34 at 1) a 1971 memorandum from Anne Alderman to Dr. R. L. Gillespie (G–23). (Ms. Alderman did not testify.) That memorandum also noted that the probit-log dose curve over the entire range of doses used could be observed in the C3H female mice in the Gass study. The interpretation of the Gass study data advanced by Drs. Condon, Cornfield and Gross is at least as persuasive as the manufacturing parties witnesses' conclusion (discussed above) that the results with the 6.25 ppb group are inconsistent with a dose.

The Alderman memorandum also contains the following observation (G–23):

> When the three lowest dosage groups (6.25, 12.5 and 25 ppb) are combined, they show a significantly ($P<.025$) higher incidence than the control group, indicating that there is evidence of an effect somewhere in this range.

Because the Gass study would not be expected to be sufficiently sensitive to produce interpretable results at levels in the 6.25 to 25 ppb range, I do not rely upon the argument by the Bureaus that this study shows DES to be a carcinogen at such low levels.

(*d*) *Conclusion As to Gass Study.* The testimony of the Bureaus' witnesses discussed above focused on the question whether the effect observed with the 6.25 ppb group in the Gass study was real. Preoccupation with the 6.25 ppb result threatens, however, to obscure the really important point about that study. No one, not even among the manufacturing parties' witnesses, disputed that this study showed that DES causes mammary cancer in mice in doses at 50 ppb and above. In fact, several manufacturing parties' witnesses agreed that there is a dose response relationship observable above that level.

If a substance causes cancer at the higher dosages in an animal assay and does not cause cancer at lower dosages, a scientifically sound interpretation of those results is that the test was not sensitive enough to detect the lower response that would be expected at lower dosages. Another conceivable interpretation of such results is, of course, that the dosages that did not cause an observed effect are not carcinogenic. Nothing in this record convinces me that the latter interpretation is the correct one and I cannot presume that it is.

I therefore do not rely upon a showing that 6.25 ppb DES did cause cancer in the Gass study. Rather, I rely upon the fact, discussed above in my evaluation of the manufacturing parties' contentions, that routine animal carcinogenicity tests currently cannot show a no-effect level for a carcinogen. (The support in the record for this proposition has been cited in my previous discussion of it.)

It is noteworthy that few carcinogens have been shown to cause cancer in animal studies at levels as low as 50 ppb, the level at which the Gass study unambiguously shows DES to cause cancer. Yet, the agency has not taken the position that no-effect levels have been established for carcinogens that do not show effects at levels that low.

The manufacturing parties, as noted, have argued that DES is different from other carcinogens because the carcinogenic effects of DES occur only at levels at which it causes physiological effects (such as ovarian weight depression (see M–62 at 3)) associated with its estrogenic activity. I have discussed in section III(D)(1) above my reasons for rejecting that theory. I must note that in any case the Gass study does not show, as the manufacturing parties contend, that there is a no-effect level for DES's estrogenic properties. An equally plausible interpretation of the data from that study is that the study was not sensitive enough to detect estrogenic effects below 25 ppb.

(ii) *NCTR Studies.* FDA's National Center for Toxicological Research (NCTR) has been performing relatively large scale carcinogenicity studies with DES. (Apparently manufacturing party Hess & Clark is also doing, or has completed, an animal DES study, whose results it has not revealed in the record (Tr. at 1460, 1469).) Neither the manufacturing parties nor the Bureaus were able to introduce evidence as to the final results of the NCTR studies. Each side, however, had witnesses testify about preliminary results that seemed to be favorable to its position.

The Bureaus introduced the testimony of Dr. Benjamin Highman of NCTR (G–54). Dr. Highman testified that he had examined tissue slide preparations of mice from one of the ongoing NCTR experiments (id. at 2). He stated that he found DES-related adenocarcinomas of the cervix and endometrium in test animals and did not find any such tumors in the control mice (id.). The number of such effects he had found as of the date of his testimony (March 22, 1977) was not large enough to be characterized as statistically significant (id.).

Dr. Highman's testimony was updated at the time of cross-examination (May 16, 1977) to include findings of additional tumors since the time when the direct examination was submitted (Tr. at 109–117). The additional information did not make the figures statistically significant (id. at 138). Dr. Highman noted, however, that the adenocarcinomas are extremely rare and he stated that the rarity itself made them significant from a pathological standpoint (G–54 at 2).

A manufacturing parties' witness, Dr. Jukes, testified that the NCTR had just completed (as of September 12, 1977) a a confirmatory experiment in which C3H mice received DES. He stated that the mice receiving 10 ppb of DES had a lower incidence of tumors than the control mice. From this information he drew the conclusion that the 6.25 ppb result in the Gass study represented insignificant fluctuation above the control value (M–99 at 5). This testimony was first stricken by the Administrative Law Judge and then reinstated (Tr. at 2141).

Dr. Jukes seems to have admitted at the time of cross-examination (November 4, 1977), that his statement that the test had been just completed was not entirely accurate, or at least did not mean that the histology and analysis had been completed (Tr. at 2140). During cross-examination, Dr. Jukes also agreed that his statement was referring only to mammary tumors and not to all tumors in the test animals (Tr. at 2206).

The question of how to deal with ongoing studies in an administrative

hearing is a difficult one. Until a test is completed and properly analyzed, reports of its results can be misleading. The FDA occasionally has to rely on preliminary analyses of test results in regulatory decisionmaking. It does so reluctantly and only in circumstances in which it has obtained all the information available about the study in question. The restrictions inherent in a regulatory hearing make full knowledge about the NCTR study impossible.

I have concluded that I should not rely upon the preliminary reports of results of the NCTR study. I have, however, considered whether my findings would change in any way if I were to accept as valid Dr. Jukes' report that the group of mice receiving 10 ppb DES in the NCTR study had a lower incidence of mammary tumors than control mice. For the reasons that follow, my findings would not change.

Dr. Jukes did not report that DES did not cause cancer in mice treated with higher levels of DES or even that those results did not show a dose-response relationship. As I have discussed, I must presume that the 10 ppb result, if reported correctly, is attributable to the insensitivity of the test system. That result alone, or together with the Gass data, would form no basis for determining that a no-effect level for DES's carcinogenicity had been identified.

(iii) *Conclusion As to Animal Carcinogenicity Data.* I find that DES is a carcinogen and that the results of the Gass study do not demonstrate a no-effect level for the carcinogenicity of DES. The NCTR data are not complete and cannot be relied upon. The results of the NCTR study reported by Dr. Jukes would not, at any rate, justify a finding that there is a no-effect level for DES. These findings warrant a conclusion that DES has not been shown to be safe and that it is unsafe.

(b) *Human Cancer Data.* It is entirely appropriate for a regulatory agency such as the Food and Drug Administration to conclude from data showing a substance to be carcinogenic in animals that that substance presents a caner risk to human beings. Indeed, FDA has done so often. See, e.g., *Certified Color Manufacturers Association* v. *Mathews*, 543 F.2d 284 (D.C. Cir. 1976) (Red No. 2); *Bell* v. *Goddard, supra* (DES as a poultry implant). The Bureaus have, in any case, presented expert opinion in this case to support the association between animal and human cancer. See, e.g., G–85 at 3 (Dr. Marvin Schneiderman). Thus, the evidence that DES is a carcinogen in humans is simply corroborative of the conceded animal carcinogenicity of DES, unless the human data can be said to show or to disprove the claim that very small amounts of DES have no effect when administered to humans. The data presented in the hearing do neither.

(i) *Dr. Herbst's Data.* Dr. Arthur L. Herbst discovered a link between the use of DES by expectant mothers as a drug to prevent miscarriage and a variety of changes in the genital tracts of female children born to those mothers. Chief in importance among these changes, which are manifested in most cases when the daughters are teenaged or older, is the finding of adenocarcinoma in the daughters' genital tracts. Dr. Herbst refers to these cancers as "clear cell adenocarcinoma," a type of tumor that he regards as rare (see, e.g., G–38).

After publication of his initial findings of a relationship between this type of cancer and maternal ingestion of DES, Dr. Herbst was instrumental in setting up and has directed a registry of clear cell adenocarcinoma in the genital tract of young females (G–37). Discoveries of this type of cancer have been reported to him and he has sought to determine whether each such cancer is, in fact, associated with maternal DES use. Dr. Herbst has reported his findings in a series of articles in medical journals (G–38 through G–43; G–45; M–26).

One hundred fifty-four of the 302 cases of clear cell adenocarcinoma reported in the most recent article were in women whose mothers had been treated with DES; 65 were not; 25 of the 302 reported cases were in women whose mothers had been treated with unidentified medication; and the history of the remaining 58 was uncertain (M–26 at 44). About 50 out of the 302 cases in his Registry were fatal. (G–37 at 3). (The Administrative Law Judge mistakenly states that 50 percent of the cases were fatal (I.D. at 25).)

Dr. Herbst referred to the "now generally-accepted relationship of these cancers to maternally ingested DES" (G–37 at 1). See also his statement that "the association of DES with these cancers is now an accepted fact" (id. at 2).

Dr. Herbst stated in his testimony that he was unable to calculate a risk figure to predict what percentage of those exposed to DES in utero will develop cancer (C–37 at 4). He stated that the "risk rate" through age 25 may be approximately 1 cancer per 1,000 exposures to the DES anti-abortion treatment, a risk that he regarded as significant (id. at 5). He declined to predict whether the rate will increase as the exposed individuals grow older (id.).

In a paper submitted by the manufacturing parties (M–26), Dr. Herbst and others utilized data obtained through his registry to make calculations of the risk of cancer from maternal DES use. These calculations are extremely questionable. They are based upon a ratio of the cases reported to him to the total number of female births during the various years in question. This ratio is then adjusted by a variety of estimates of the percentage of the total births in a given year that involved the administration of DES to the mother. It would appear obvious that the numerator (number of cases of this kind of cancer) would not represent all of the cases of this cancer during the years in question and that the denominator (number of births involving DES treatment of the mother) is based on speculation. The risk figure computed (for subjects 24 years old and younger) is between 0.14 and 1.4 per 1,000 (M–26 at 47). The only possible value of these calculations would be as an illustration that the number of DES-related vaginal tract cancers in proportion to the number of females exposed in utero is relatively small.

The Administrative Law Judge's decision summarizes the Herbst data, but does not discuss the manufacturing parties' attacks upon that evidence. Those attacks are four.

First, the manufacturing parties argue that Dr. Herbst has not shown a carcinogenic effect caused by DES. The manufacturing parties argue that the effect observed is teratogenic rather than carcinogenic (Manufacturing Parties' Exceptions at 142–144). Dr. Herbst himself has stated that the effect *may* be teratogenic (G–41 at 17 Tr. at 1165–66). This is also the conclusion of the manufacturing parties' witness, Dr. Jensen (see M–69 at 12). The teratogenic effect would be an alteration in the vaginal tract during the growth of the embryo that would lead occasionally to cancer (id.). The importance of this distinction is that a teratogenic effect leading to cancer would not be evidence that DES would cause cancer in those not exposed in utero. On this record, I have insufficient basis to determine that the effect observed cannot be characterized as carcinogenic. But in any case, a teratogenic effect would be a sufficient basis for a finding that DES is not shown to be safe.

Second, the manufacturing parties attempt to discredit the association between maternal use DES and the effects observed (Manufacturing Parties' Exceptions at 144–146). During cross-examination, Dr. Herbst was asked whether he knew what proportion of the mothers of affected daughters were diabetics or were taking insulin or were subject to high blood pressure. Dr.

Herbst answered that he did not know the specific figures, but that few were diabetic (Tr. at 1158–59). Dr. Herbst's responses to questions asked on cross-examination demonstrate that he did, in fact, look for other potential causitive factors for the cancers (id. at 1159, 1162). The manufacturing parties' attack on his data on that ground is thus not persuasive.

On cross-examination, Dr. Herbst stated that a high proportion of DES-treated mothers had a history of previous abortions or bleeding as a complication of pregnancy (Tr. at 1159). Since DES was used to prevent abortions, this fact would be expected (cf. Tr. at 1155, 1158). Manufacturing parties' witness Dr. Kliman appeared to suggest that the cases of vaginal adenocarcinoma found by Herbst might be associated with the saving of otherwise "high risk" pregnancies (M–110 at 21–22). Dr. Kliman criticized the failure of Dr. Herbst to compare his findings to a control group of comparable individuals (id. at 22). Dr. Kliman argued that the best control group would have been siblings of the treated mothers (apparently those siblings carried by the mothers during a time when they were not treated with DES (id. at 21–22)). Since, he apparently theorized, all these children would be dead (id.), by his definition such a comparison could not be made.

Dr. Kliman's argument is based upon speculation that there is some correlation between the need for DES as an anti-abortion agent and the cancer observed. He does not suggest a basis for this theory. Thus, while Dr. Kliman has pointed to another variable that cannot be controlled in the analysis of the Herbst data, his arguments do not form a basis for disregarding the association that Dr. Herbst has observed.

The manufacturing parties' third criticism of Dr. Herbst's data is that is shows effects only at "extremely high dosages" (Manufacturing Parties' Exceptions at 146–148). They argue that the Herbst data do not show a dose response relationship with DES and thus do not show that very small doses of DES cause a response. Dr. Herbst had identified one case in which the mother had received as little as 1.5 mg of DES per day or 135 mg during the entire pregnancy (G–39 at 716; G–37at 4), but the manufacturing parties argue that this result is consistent with the hypothesis that low amounts of DES do not cause the effects Herbst observed. They would lump this low dose case with cases reported for which there is no evidence that the mother was administered DES. Apparently the manufacturing parties are suggesting that all the other cases of DES-related cancers reported by Herbst involved very large doses of DES. Dr. Kliman testified that the usual dose for anti-abortion therapy was 5 to 150 mg per day (M–110 at 22).

The argument about size and dosage becomes important in light of the manufacturing parties' argument that any cancer-causing effect of DES is associated with its estrogenic properties. (See discussion of this question in section III(D)(1) above.) Thus, they argue that the dosage of DES administered as medication would be much greater than the amount of endogenous estradiol that humans normally produce (M–69 at 10). The amount of DES that might be consumed daily through ingestion of part per billion residues of DES in meat, on the other hand, would not add significantly to the amount of endogenous estradiol (id. at 10–11). As discussed in section III(D)(1), however, DES differs significantly from other estrogens.

The fourth manufacturing parties' attack on the Herbst data involves the charge that those data do not demonstrate a distinction between DES and natural estrogens (Manufacturing Parties' Exceptions at 148–149). Dr. Jensen argued that animal data show that abnormalities in developing reproductive organs, including production of tumors, can be induced with natural steroidal estrogens as well as with DES (M–69 at 14, 15). As discussed in section III(D)(1), however, DES is in some ways significantly different from natural estrogens. In view of these differences, I can not assume that natural estrogens, if used as DES was used in the treatment of pregnant women, would result in the abnormalities in their offspring observed as the result of usage of DES.

The attacks on the Herbst data, and on the conclusion that these data show an association between DES and cancers in humans, are thus without merit.

(ii) *Mayo Clinic Data.* In a study supported in part by FDA and NIH, 1,719 children born to mothers who had used DES during pregnancy at Mayo Clinic obstetric facilities from 1943 through 1959 were followed to determine whether any had developed cancers. No cancers of the vaginal or (for males) urinary tract were found. The authors of the report of this followup project concluded that their findings did not show a lack of correlation between DES and the vaginal tract cancer observed by Herbst. Rather, they concluded that their work showed the association to be rare (G–44 at 797).

The researchers calculated the upper limits of the risk from the use of DES as a carcinogen that would be consistent with their findings of no such cancer in 803 live born females. They calculated an upper risk limit with a 95 percent confidence level of 4 cancers per 1,000 exposed subjects (G–44 at 798). The researchers also considered the potential risk if their study were limited to those children of mothers exposed to DES during the first trimester of pregnancy. (The cases observed by Herbst had involved such exposure.) Using this group, and adjusting for the age of the patients at the time of followup, the researchers calculated an upper limit risk of 7 per 1,000 of developing this kind of cancer by age 13 and a risk of 13 per 1,000 of developing the cancer by age 22 (id.). It must be remembered that the results of this followup study are also consistent with a risk of zero per 1,000 for any of the groups considered. The upper risk limit is merely a function of the number of persons included in the followup group.

I accept the researchers' conclusion about this study—that it does not show that there is no association between maternal DES therapy and vaginal tract cancer in offspring but that it does show that that association is relatively rare.

(iii) *Chicago Study.* The University of Chicago sponsored a followup study of a controlled efficacy trial for DES use in pregnancy that had been conducted during 1951 and 1952. A report of early findings in this study was published in January 1977 and included in the record (G–10). A later, unpublished report of further progress of the study, submitted by the researchers to their contract monitor on August 31, 1977, was added to the record later (G–192). Each report states that no statistically significant correlations between cancer and DES treatment had been observed, either in the mothers treated or in the children exposed in utero. (There were other, noncancerous, effects of treatment. See section III(D)(3) of this Decision below.)

There were differences in the cancer incidences between the DES mothers and their control counterparts: 4.9 percent of the DES exposed women contracted breast cancer while 3.1 percent of the control women were similarly afflicted; 5.9 percent of the DES exposed women had cancer in "endocrine related sites" (breast, endometrium, ovary, and colon), while 4.2 percent of the control women had such cancers; 3.6 percent of the DES exposed women had cancers at other sites, while 2.7 percent of the control women had such cancers (G–192, Appendix 4–15a). None of these

increases was statistically significant, however.

The Bureaus, in their brief to the Administrative Law Judge, argued that G–192 illustrates that the increased risk of cancer in the DES exposed mothers was significant over time, i.e., that the DES mothers contracted cancer earlier than the control mothers (Bureaus' Brief at 34). Though the results reported do show that DES-treated mothers developed breast cancer earlier than women in the treated group (G–192, Appendix 4–14a), there is no showing that this effect is statistically significant.

The manufacturing parties submitted a statement of Dr. Herbst on this issue (M–209). In this proffered testimony, which was not received in evidence by the Administrative Law Judge, Dr. Herbst stated that he was now the principal investigator on the University of Chicago followup study, replacing Dr. Bibbo, who had authored G–192. Dr. Herbst stated that he, Dr. Bibbo, and the biostatistician involved in the research project agreed that G–192 did not establish that DES ingestion by mothers during pregnancy had caused an increased risk of breast cancer or that the report otherwise was evidence of carcinogenicity of DES in humans.

I concur with Dr. Herbst's analysis of this study. The data from the Chicago study taken alone would not be a basis for a finding that DES is a human carcinogen. Those data are, however, not inconsistent with that proposition. The results referred to by the Bureaus do raise questions about whether a larger, and thus more sensitive, study might show the effects the Bureaus contend exist.

(iv) *Conclusion as to Human Cancer Risk.* I find that evidence in the record concerning the incidence of clear cell adenocarcinoma in daughters of mothers treated with DES (the Herbst data) supports the conclusion (which may also be drawn from animal carcinogenicity data) that DES presents a human cancer risk. The evidence from the treatment of women with DES provides no basis for concluding that there is a no-effect level for DES with respect to cancer. These findings warrant the conclusions that DES has not been shown to be safe and that it is unsafe.

(3) *Adverse Effects of DES Other Than Cancer.* As noted above, the "safety clause" must be invoked if serious questions about the safety of observed residues are raised by the Bureaus, and the manufacturing parties fail to show that the DES residues are safe. I find that safety questions about DES have been raised not only by the substance's carcinogenic effects but also by other adverse effects with which it is associated. These questions have not been resolved.

(a) *Teratogenic Effects.* Dr. Thomas Collins of the Bureau of Foods testified about his review of articles suggesting a teratogenic effect associated with DES (G–12). He defined "teratology" as the science concerned with the generation of structural or functional alterations or malformations in organisms during their development, both prior to and subsequent to birth (id. at 1).

Based upon his review, Dr. Collins gave his opinion that DES is a teratogen in mice and humans and that it has specific effects on male and female reproductive systems and on the cardiovascular system (G–12 at 6; see also G–57 at 5; G–72 at 7–8). He based his conclusion on the following: (1) observations of anomalies of cervix development in females after prenatal exposure to DES (see discussion in this section below); (2) reproductive tract lesions in male mice exposed prenatally to DES in a study by McLachlan, et al. (see discussion in this section below); (3) observed effects on male genital tracts associated with the administration to the subjects' mothers of DES prior to the subjects' births (also discussed in this section below); (4) a letter to *Lancet* (the British Medical Journal) reporting one case of functional incompetence of male gonads, apparently associated with human prenatal DES exposure; (5) a report that four female human infants and children exposed to DES in utero exhibited a degree of masculinization, in a report that also stated that the offspring of 700 DES-treated women were shown to be normal; (6) three studies demonstrating teratogenicity of DES and DES dipropionate in mice; (7) a report that cardiovascular malformations were found at birth in children exposed prenatally to oral contraceptives during the first month of pregnancy at the rate of 18.2 per 1,000 versus 7.8 per 1,000 among children not so exposed. The reports relied upon by Dr. Collins are found in the administrative record at G–13 through G–20.

The manufacturing parties' Dr. Bernard Kliman contended that Dr. Collins' summary of published articles on the teratogenicity of DES is worthless "because he has failed to provide any analysis of these reports" (M–110 at 19). Dr. Kliman contended that these reports do not support Dr. Collins' statement that DES is a teratogen (id.). His own review of these reports was rather sketchy, and the criticisms he makes of them are not persuasive. Dr. Kliman discounted, for example, the three studies of Gabriel-Robez and colleagues (G–17, G–18, G–19) (the sixth basis for Dr. Collins' opinion as cited above) because DES dipropionate was administered instead of free DES (M–110 at 19)). DES dipropionate is, however, hydrolized by esterases (enzymes which catalyze the hydrolysis of esters into their alcohols and acids) to yield DES and propionate. Due to the abundance and ubiquity of these esterases, the proposition that DES was the underlying cause of the observed teratogenic effects cannot be disregarded.

One of the articles by Dr. Herbst details the benign abnormalities of the vaginal tract found in a study of 110 DES daughters and a control group of 82 unexposed females (G–40). He found an association with very high statistical significance ($p = <.0001$) between DES and the following abnormalities: vaginal or cervical fibrous ridges; cervical erosion identified in biopsy specimens; failure of part of the cervix to stain with iodine; vaginal adenosis identified in biopsy specimens; failure of part of the vagina to stain with iodine (id., Table 3).

These and other noncarcinogenic abnormalities observed in the daughters of DES-treated mothers may be characterized as "benign" (G–40 at 338). Any change in the human body caused by the administration of a foreign substance is, however, reason for concern. Although there is apparently no evidence of the direct transition from adenosis (the presence of glandular epithelium or its mucinous products), one of the observed abnormalities, to adenocarcinoma, it is noteworthy that adenosis is present in nearly all of the adenocarcinoma victims (id. at 339; see also G–42 at 10; cf. G–138 at 3).

Dr. Gill, in reporting his followup study of a controlled test of the effectiveness of DES in pregnant women (the Chicago study (G–10)), also observed statistically significant associations of maternal ingestion of DES with circumferential ridges of the vagina and cervix and dysplastic lesions in these tissues in female offspring. This study also demonstrated with statistical significance ($p<.01$ and $p<.005$) that DES is related to observations of epididymal cysts (the epididymis is the cordlike structure, near the testis, whose ducts store the spermatazoa), and hypotrophic (underdeveloped) testes in the male offspring. In addition, a substantial percentage (28) of the group of males exposed to DES in utero had severely pathologic decreases in sperm production; no such effect was found in the control males. Dr. Gill reported adenosis in 66.8 percent of the DES-exposed females compared to 3.6 percent in the control group. A later

report of this study (G–192), which includes more data, also found significance in these areas.

Dr. John McLachlan was an author of a book chapter (G–61) dealing with the transplacental toxicity of DES. It details a number of animal and human reports that have shown problems with the in utero exposure of animals and humans to DES. Some of the articles cited have been included in the administrative record. For example, G–60 is a report of a test of male mice exposed in utero to DES (100 mg per kg of maternal body weight administered daily from day 9 through day 16 of gestation). Six of 10 males born of DES-treated mothers were sterile, while none of a similar size group of males born to control mothers was sterile. Upon sacrifice, 15 of 24 of the males born to DES-treated mothers and none of the 15 males born to control mothers was found to have testicular changes (id. at 991).

Dr. McLachlan testified that carcinogens that require long term, high dose administration to induce detectable cancer in adult test animals have been shown to be capable of producing cancer in offspring of treated mothers at much lower doses administered for shorter periods of time (G–59 at 2). He identified this phenomenon as transplacental carcinogenicity and suggested that the human carcinogenicity data discussed above show DES to be a transplacental carcinogen (id.).

Dr. McLachlan is performing a series of studies on the teratogenic effects of DES (id. at 5). He described one such study, in which he observed a statistically significant dose response relationship between DES administration and loss of fertility of female progency of DES-treated mothers in a mouse study (id. at 4). The dosages range from 0.01 to 100 micrograms (μ) per kilogram (kg) of animal body weight. Although there was no statistically significant difference between the lowest dosage and the control animals, the dose-response relationship observed and the fact that higher levels caused an effect is significant.

Dr. Kliman objected to Dr. McLachlan's studies because "no control experiments were conducted with any natural estrogen (M–110 at 14), so that it is impossible to determine whether the observed effects would also have been caused by natural estrogens. However, Dr. McLachlan's objective was to ascertain the transplacental toxicity of DES, in which he succeeded, and not to establish that DES is the only estrogen that exhibits transplacental toxicity.

Dr. McLachlan described a theory that would differentiate DES from other estrogens with respect to transplacental toxicity:

> In the normal pregnant female, the presence of high levels of the endogenous estrogens may be less of a threat to the developing fetus because of the presence of *alpha*-fetoprotein, a substance that acts as a high affinity binder of natural estrogens and so renders them relatively nontoxic to the fetus. It has been demonstrated that DES does not bind to *alpha*-fetoprotein with the same high affinity (id. at 5).

In addition, he cited the same type of relationship in mammals for TeBG (discussed in section III(D)(1) above). For this and other reasons (id. at 6), it was his opinion that DES plays a more critical role than the endogenous estrogens in transplacental toxicity.

According to the manufacturing parties' Dr. Bernard Kliman, Dr. McLachlan misinterpreted the data of Uriel, et al. (G–63) in developing his theory. Dr. Kliman stated that DES has 40 percent of the activity of estradiol and nearly the same activity as estradiol in binding to these proteins. Also, the lower binding activity of DES only allows DES to be metabolized more quickly by the liver (M–110 at 15–16).

As discussed in section III(D)(1) of this Decision, data sufficient to resolve the arguments presented by Dr. McLachlan and those presented by Dr. Kliman on this issue is lacking. It is therefore not possible to determine with assurance that the teratogenic (or mutagenic) effects of DES either differ from or are the same as the effects associated with endogenous estrogens.

I must conclude, on the basis of the evidence discussed in this section, that DES is a teratogen in animals and in humans.

(b) *Mutagenic Effects.* Dr. Sydney Green, who, at the time of his testimony, headed the Genetics Toxicology Branch of the Division of Toxicology, Bureau of Foods, reviewed two published reports (G–32 and G–33) that establish the mutagenicity of DES diphosphate. The first study revealed that DES diphosphate resulted in monosomies (cells with one chromosome less than normal) and trisomies (cells with one chromosome more than normal) in the bone marrow of mice (G–32). Dr. Green classified this as a mutagenic effect (G–31 at 2):

> The monosomies are not significant contributors to hereditary diseases or disorders because cells possessing such chromosomal abnormalities rarely survive. However, the presence of trisomies can be said to be a true mutagenic effect. Such cells usually survive and pass on their abnormal characterisitcs to future generations. If these effects are seen in germinal (sex) cells they can lead to mongolism and other hereditary disorders.

The second study also uncovered the production of trisomies in offspring of mice whose mothers were treated with DES diphosphate (G–33).

During cross-examination, Dr. Green stated his opinion that DES could be considered as the underlying cause of this mutagenic effect (Tr. at 578–79). He noted, among the bases for his opinion on this issue, the fact that when DES diphosphate is hydrolized it yields DES: "So, in essence, one would be testing diethylstilbestrol within the cells, as opposed to diethylstilbestrol diphosphate"(Tr. at 579).

Dr Kliman criticized the testimony of Dr. Green, particularly because Dr. Green failed to mention that similar mutational aberrations are also associated with the natural estrogens (M–110 at 20). But, during cross-examination, Dr. Green acknowledged that studies have shown estrogens to be mutagenic (Tr. at 578–79). Like Dr. McLachlan, he did not claim DES is the only estrogen that produces adverse effects.

I find, on the basis of the evidence in this record, that DES does cause mutagenic effects in some circumstances.

(c) *Other Effects.* Dr. Roy Hertz reported on the extreme potency of DES evidenced by accidental absorption in industry and the home, such as "the occurrence of breast development in children ingesting accidentally DES contaminated vitamin capsules," and "the precocious development of the breasts and external genitalia when the prepubertal daughter of a worker (in the animal drug industry) used her father's bed while he was at work" (G–46 at 7). These reports add marginally to the impression that DES poses genuine and serious risks to humans and that its activity produces toxic effects that are not now totally understood.

(d) *No-Effect Level.* The Bureaus' witnesses testified that no-effect levels for the adverse effects of DES could not be established. With regard to the teratogenic effects of DES, Dr. Collins testified that "none (of the reports he evaluated) are sufficiently complete to allow us to establish safe tolerance levels for DES" (G–12 at 6). Dr. Gill, who reported on the effects of DES discovered in the Chicago study, stated that "it is not possible to calculate a safe tolerance level for such exposure for the data reported" (G–138 at 3; see also G–37 at 5).

Dr. Kilman testified that Dr. McLachlan's work points to a no-effect level of DES because "female mouse

fertility was not significantly altered by the lowest dose, 0.01 μg per kg per day on days 9 to 16 of pregnancy" (M–110 at 14–15). The failure of this test to demonstrate a response at its lowest dosage could, however, be the result of the relative lack of sensitivity of the test system. Dr. McLachlan himself testified that it is not possible to determine a no-effect level from his studies (Tr. at 92).

Dr. Green testified that the mutagenic studies he reviewed also did not support the existence of a no-effect level for DES:

> These studies, however, do not provide quantitative data which would allow a calculation of a no-effect level for these effects and the subsequent estimation of safe tolerance levels for humans (G–31 at 3).

(e) *Conclusion As to Adverse Effects of DES Other Than Cancer.* I find that the evidence presented by the Bureaus demonstrates that DES is a teratogen and a mutagen. It is not possible from the evidence in this record to establish the existence of a no-effect level for DES for these effect. Thus, the fact that DES causes teratogenic and mutagenic effects is an independent basis for my conclusion that DES has been shown not to be "shown to be safe," and that it is unsafe, for its approved uses.

(E) *The Risk-Benefit Issue* (1) *Propriety of Risk-Benefit Analysis.* The Administrative Law Judge held that under 21 U.S.C. 360b consideration of the alleged societal benefits of the use of DES is not an appropriate part of the decision whether approval of the new animal drug application should be withdrawn (I.D. at 15). This interpretation of the statute is supported by the legislative history of the statute, is consistent with positions the agency has taken previously on this issue, and reflects sound public policy. In *Hess & Clark, Division of Rhodia, Inc.* v. *FDA,* 495 F.2d 975 (D.C. Cir. 1974), however, the Court stated in *dictum* that the FDA should consider the benefits of the use of DES should it proceed under the "safety clause" (495 F.2d at 993–94):

> Outside of the per se rule of the Delaney Clause, the typical issue for the FDA is not the absolute safety of a drug. Most drugs are unsafe in some degree. Rather, the issue for the FDA is whether to allow sale of the drug, usually under specific restrictions. Resolution of this issue inevitably means calculating whether the benefits which the drug produces outweigh the costs of its restricted use. In the present case, DES is asserted to be of substantial benefit in enhancing meat production, and this is not gainsaid by FDA. The FDA must consider, after hearing, whether DES pellets would be safe in terms of the amounts of residue consumed. (Footnotes omitted.)

Early in 1977, the manufacturing parties filed a motion in the United States Court of Appeals for the District of Columbia Circuit to compel the agency to consider the societal benefits from DES, including any adverse environmental consequences from withdrawal of the NADA's, as part of the hearing. In a memorandum of March 22, 1977, Acting Commissioner Gardner mooted that question by directing the Administrative Law Judge to consider the benefits issues. He did so by means of a memorandum to the Administrative Law Judge in which he noted that he was taking no position on the relevance of these issues to the proceeding. He did state in that memorandum: "In making this safety determination [under the "safety clause"] societal benefits and environmental effects have historically not been considered to be legally relevant" (Record No. 110 at 2).

(a) *Legislative History.*— (i) *New Animal Drug Provisions.* The new animal drug applications that are the subject of this hearing are creatures of the animal drug amendment of 1968. As noted in section I, that amendment was intended to consolidate the agency's review of animal drugs, which was at that time being conducted under the food additive amendments and the new drug provisions. Congress did not, in writing the new animal drug provisions, include language authorizing the FDA to consider the benefits of an animal drug in determining whether it is safe. (Compare 21 U.S.C. 346 and 346a, in which Congress required the Commissioner and (now) the Administrator of the Environmental Protection Agency to consider the benefits of the products regulated under those sections in the setting of tolerances.) Nothing in the legislative history of the 1968 amendments supports the proposition that the FDA should consider the socio-economic benefits of a drug in deciding whether it is safe. The manufacturing parties have, however, relied upon legislative history of the new drug and food additive provisions for support of their position that benefits should be considered. Little support exists.

(ii) *New Drug Provisions.* DES was approved for animal use in the 1950's under the then-existing new drug provision. Prior to 1962, when effectiveness was made an additional consideration, new drug applications were approved if use of the drug was shown to be safe. At that time, the agency took the position that effectiveness was an element in the consideration of the safety of a drug when that drug was to be used in treatment of a life-threatening disease or where there was an indication that that drug would occasionally produce serious toxic or even lethal effects. The manufacturing parties argue that, in taking this position, the FDA was stating its understanding that a safety determination necessarily involved a risk-benefit analysis.

The evident flaw in the application of the manufacturing parties' argument to the instant proceedings is that effectiveness in a human drug context is different from effectiveness in an animal drug context. The risk to the patient from a human drug may be justified by a therapeutic benefit *to that patient* from the drug. It is an entirely different question, however, whether the risk to human consumers of the products of animals are justified by an economic benefit to animal drug manufacturers, animal producers, or meat consumers generally.

(The only time where the theory that effectiveness is part of safety would be applicable to an animal drug would be circumstances in which the risk was to the animal itself, as opposed to any human consumer. FDA considers that type of benefit relevant to a determination of safety; but that type of benefit is not at issue in this proceeding. The types of benefits urged by the manufacturing parties are alleged health benefits to humans and economic and environmental benefits.)

There is, of course, an obvious difference between the therapeutic benefits of a drug, which often alleviate a risk to the person to whom the drug is administered, and so-called "socio-economic" benefits associated with the use of a drug. The former are the *only* type of benefits that the FDA considers in determining whether a human drug is safe. The agency never considers socio-economic benefits in making that decision.

Moreover, the consideration of risks and benefits with respect to human drugs is always based on the premise that before being exposed to the risk, an individual patient will have the protection of either a physician's evaluation (in the case of a prescription drug) or adequate directions for use enabling the patient himself to decide whether to run the risk (in the case of an over-the-counter drug). No such protection is available to those exposed to the risk from residues of DES in meat.

The asserted similarity between the treatment of human drugs and animal drugs is, of course, critical to the manufacturing parties' argument on this subject. Apparently the distinction between the two systems of regulation was not adequately pointed out to the

Hess & Clark Court, however. In a footnote, the Court quoted extensively from an article by Richard Merrill on prescription drug injuries as support for the proposition that effectivenss considerations are relevant to safety determinations (495 F. 2d at 994 n. 59).

(iii) *Food Additive Provisions.* The manufacturing parties rely upon the fact that one impetus for passage of the food additives amendment was a desire by the FDA and the regulated industry to allow FDA to set tolerances for products that were hazardous at some levels and not at others. Congress, in accommodating this desire by allowing the setting of tolerances, allowed the agency to consider the level of the ingredient that would be required to serve its functional purpose. Where a tolerance limitation is required for a product, the tolerance may not be greater than the amount necessary to accomplish the additive's intended purpose; see 21 U.S.C. 348(c)(4)(A). Similarly, where a tolerance is required, no food additive petition may be approved unless it contains evidence that establishes that the additive will accomplish its intended physical or other technical effect; see 21 U.S.C. 348(c)(4)(B).

Thus, where an additive is shown to be safe at some level, the FDA is authorized to consider whether it does what it is intended to do. The FDA is not, however, authorized to consider whether what the additive is supposed to do provides any benefit to society. Congress was explicit in its reports on this bill that the FDA would not be allowed to consider the societal benefits to be derived from use of the food additive in question. See, e.g., S. Rept. No. 2422, 85th Cong., 2d Sess. 7 (1958): Determination of a proper tolerance level "does not involve any judgment on the part of the Secretary of whether [the food additive's] effect results in any added 'value' to the consumer of such food or enhances the marketability from a merchandising point of view." *Accord,* H.R. Rept. No. 2284, 85th Cong., 2d Sess. (1958). (Congress thus rejected the position apparently advanced by Commissioner of Food and Drugs Larrick in 1956 that some consideration of the "benefit to the producer or consumer" should be permitted in the evaluation of food additives, Hearings Before Subcommittee of the House Interstate and Foreign Commerce Committee on H.R. 4475, etc., 84th Cong., 2d Sess. 194–95 (1956).) Therefore, under the food additive amendment, were a tolerance applicable for a substance such as DES, FDA would be barred from considering societal benefits in setting that tolerance.

(ii) *Conclusion As to Legislative History.* Congress thus did not authorize or require consideration of the socio-economic benefits of an animal drug in determining its safety. Indeed, the language adopted by Congress, having its roots in the human drug and food additive provisions of the law, clearly reflects an intention that FDA definitely not consider socio-economic benefits in making decisions on the safety of animal drugs. I thus conclude that Congress has made the determination that an animal drug that poses a risk to humans can never be considered "safe" because it provides an economic or other social benefit to society.

(b) *The Agency's Position.* The FDA has never considered the benefits of an animal drug that posed a risk to ultimate human consumers when deciding whether that drug is safe. The manufacturing parties do not contend that the agency has done so. Indeed, *Bell* v. *Goddard, supra,* which also dealt with DES—there as a drug for poultry—describes an FDA action with respect to an animal drug in which not even the proponents of the drug contended that benefits should be considered.

The manufacturing parties do quote from the preamble to regulations issued by the FDA in 1976 that deal not with animal drugs but rather with food additives. As first proposed in September of 1974, these regulations would have defined "safe" and "safety" to include consideration of, among other factors, "[t]he benefit contributed by the substance" (39 FR 34194 (September 23, 1974)). When the final regulations were issued, this consideration was deleted. In an apparent attempt to explain the agency's rationale for the original proposal, however, the preamble to the final regulation made the following statement (41 FR 53601; December 7, 1976):

> The Commissioner concludes that it is appropriate to recognize that the benefit contributed by a substance is inevitably a factor to be considered in determining whether a particular substance is "safe" (or generally recognized as "safe") for its intended use. The term "safe" is to be given its ordinary meaning, and in its common usage the term is understood to carry an assessment of benefits and risks. It is true, as the comment states, that minor food additives are not approved at levels that may present a hazard to the normal consumer. This result is required by the act because the benefit of a minor food additive is too small to justify the imposition of a known risk to normal consumers; use of such ingredient at levels that may present a hazard to the normal consumer would not be "safe." However, this result does not necessarily follow in the case of important food additives. For example, if it were found that a major food source such as meat or grain was associated with the development of chronic diseases in normal individuals, it would not necessarily follow that the food was unsafe within the meaning of the act. The ordinary understanding of the term "safe" would require some benefit-to-risk analysis in such circumstances.
>
> Another example relates to the incidence of allergic reactions to particular food ingredients. Adverse reactions caused by allergy are clearly a consideration in determining whether a food ingredient is safe. Ordinarily, the incidence of allergic reactions from a food additive cannot be considered because data and test protocols do not exist. When data exist, however, they may be considered, and an assessment of benefits and risks becomes relevant. For example, if it were determined that both a particular emulsifier and a particular fruit resulted in the same unusually high incidence of allergic reactions, one might reasonably conclude that the emulsifier was not safe but that the fruit was safe. Such conclusions would simply represent common understanding of the safety * * *
>
> The Commissioner has, however, deleted from the regulations the reference to consideration of benefits on the ground that this separate consideration is legitimately included within the concept of safety as used in the act. Furthermore, explicitly retaining the criterion of benefit in the regulations might be construed as requiring routine formal analysis of a factor that the agency will only occasionally need to take into account, because the agency's general guidelines will result in disapproval of food additives that may cause toxic effects in normal individuals.

This language is quoted in full because I am, on behalf of the FDA, disavowing it. It has never been the basis for an agency decision. As discussed, there is no justification for such a statement either in the statute itself or in its legislative history.

The manufacturing parties argue that this statement in the preamble to a regulation is an advisory opinion binding upon the agency. They cite for this proposition 21 CFR 10.85(d) (1) and (e). Subsection (d)(1), in fact, does identify the preamble to a final regulation as an advisory opinion. Subsection (e) states that an advisory opinion "obligates the agency to follow it until it is amended or revoked." An advisory opinion may, however, be amended or revoked in the Federal Register at any time after it has been issued (21 CFR 10.85(g)). To the extent that the language quoted above may be considered such an "advisory opinion," that opinion has been superseded (and, by virtue of 21 CFR 10.85(g), revoked) by at least one subsequent Federal Register statement that directly contradicts it. See 42 FR 19996 (April 15, 1977) (Saccharin and Its Salts): "The

Commissioner/ * * * notes that under the provisions of the law relating to food additives, FDA is not empowered to take into account the asserted benefits of any food additive in applying the basic safety standard of the act." In any case, the language cited by the manufacturing parties deals with safety in the context of GRAS substances and food additives, not in the context of new animal drugs. It thus would in no case be binding in this proceeding. Nor could it be said that the manufacturing parties have relied on the cited language or that may disavowal of that language is in any respect unfair to them.

(c) *Policy Arguments.* There are persuasive policy arguments against having an administrative agency such as the FDA make the kind of risk-benefit analysis sought by the manufacturing parties here. It may be that preliminary issues in this analysis are of the type that the FDA is qualified by experience and expertise to resolve. The agency is equipped, for instance, to evaluate calculations of the risk from a drug such as DES if the necessary data are available (they are not here). Once the risk and the benefits of an animal drug are determined, however, the ultimate issues require pure value judgments. (On the difficulty such judgments present for the administrative process and for judicial review, see Cooper, "The Role of Regulatory Agencies in Risk-Benefit Decision-Making," 33 Food, Drug, Cosmetic L. J. 755 (1978).)

It may be suggested that the agency makes risk/benefit analyses often with respect to such products as human drugs and medical devices. This suggestion is, however, incorrect. Properly understood, the agency's evaluation of, for example, a human drug is a comparison of risk to risk. The risk of using the drug is weighed against the risk of not using it. Moreover, the risks and benefits (or avoidance of other risks) are of the same type (relative to health), accrue to the same persons (patients), and are subject to a well-established scientific and professional discipline (medicine). Even so, this type of evaluation is rarely easy. Often a calculated risk of one harm must be weighed against a significantly smaller risk of a much greater harm, as with a useful drug that occasionally produces severe side effects. The factors considered are all detriments to the public's health, however, and the decision may be appropriately considered to be a medical one.

Here, however, the manufacturing parties ask the FDA to weigh a risk of cancer and other serious adverse effects against an economic benefit. Arguably, the persons at risk also receive part of the economic benefit because the meat they purchase may be available at a lower price because of the use of DES. But much of the economic benefit, as evidenced by the tenacity with which the withdrawal of the DES NADA's has been fought, goes to parties other than the consumers of the meat products of DES-treated animals.

Perhaps society is willing to expose all of its meat-consuming members to a relatively small risk of cancer and other adverse effects in order to provide a small economic benefit to those consumers and a larger economic benefit to DES producers and, potentially, users. The FDA is not, however, qualified in any particular way to make that value judgment for society. The value judgment could not be supported by a record; a record could support only factual findings, not value judgments. Nor could the value judgment be effectively reviewed by a court, which in general is limited to consideration of facts, law, and procedures. In a democratic system, the appropriate place for value judgments to be made is the legislature. Here, as discussed above, it is apparent that Congress has shouldered the responsibility for resolving this issue. It has decided that no economic benefit justifies use of an animal drug that presents an identifiable risk to the health of consumers.

The manufacturing parties also ask FDA to consider general nontherapeutic health benefits from the use of DES. Nothing in the language or legislative history of the statute or in FDA's prior interpretation or application of the statute suggests that consideration of such benefits is either required or permissible. There is nothing to suggest that Congress or FDA has ever thought that such benefits might flow from the administration of drugs to animals. Thus, it is understandable that Congress did not contemplate that FDA would consider such benefits in determining the safety of animal drugs, and that FDA has not done so.

The argument that FDA *should* consider such benefits appeals to some as a public policy but that appeal can hardly outweigh the combined force of language, legislative history, and agency practice that weighs *against* consideration of such benefits. In view of the importance of the question, I believe it should be resolved only on a record that squarely presents it. Here, as discussed in sections III(E)(2) (c) and (d), the manufacturing parties have not shown that DES presents health benefits that could outweigh its risks. The quality of the evidence in this record on health benefits is so unsatisfactory that it does not provide a sufficiently powerful policy argument for raising the legal issue. Therefore, I would rather leave the legal question open, while recognizing that it would require a very powerful showing indeed to outweigh the strong legal arguments against consideration of such benefits.

(d) *Conclusion As to Proprietary of Risk-Benefit Analysis.* The law is clear that the FDA may not consider socio-economic benfits in the determination of the safety to human beings of a new animal drug, and I am not prepared to conclude that it permits consideration of human health benefits. In order to provide as complete a record for judicial review as possible, however, I will discuss, as did the Administrative Law Judge, the evidence presented at the hearing with respect to both types of benefits.

(2) *Risk-Benefit Analysis.* It is clear that the applicant has the burden of showing that an animal drug is "safe." If a risk/benefit analysis were appropriately a part of an animal drug safety decision, the applicant would, therefore, have the burden of showing that the benefits of the drug outweigh its risks. The allocation of the burden of proof is important because the record of this proceeding is totally inadequate even to determine what the risks and benefits of DES are (or how great the risk of DES use is), much less to provide any guidance on how the weighing of risks against benefits should be accomplished.

(a) *Quantitative Risk Assessment.* Some manufacturing parties' witnesses extrapolated from the Herbst data to calculate extremely low levels of risk of human cancer in females from the ingestion of DES-contaminated meat (see M-83; M-99; M-104). (These risk calculations do not address the question of how great a risk DES poses to human males.) Other manufacturing parties' witnesses argued that there is, in effect, no risk from the present uses of DES (M-69; M-40). For the reasons discussed below, I do not regard either of these contentions as valid. In addition, I find that the data on DES are too meager to allow any risk calculation acceptable for the purpose of supporting continued approval of DES as an animal drug.

(i) *Calculations From Herbst Data.* Dr. Herbst testified that he regards risk estimates based on his data as highly suspect (G-37 at 5):

> I am informed that others have attempted to calculate and extrapolate risk estimates and "no-effect levels" in the whole United States population for DES in food using data from our Registry, but I do not believe these calculations can properly be made from our

data, nor that "no-effect levels" can be extrapolated from our epidemiological observations of effect levels.

I agree with Dr. Herbst's opinion on this issue. The manufacturing parties' risk assessments from the Herbst data merely demonstrate that the results of a risk calculation are dependent on the assumptions on which it is based.

The following assertions about the risk of DES should be read in light of the unsupported assumptions upon which they rely, i.e., that (1) the only cancer DES causes in women is vaginal adenocarcinoma in the daughters of DES exposed mothers; (2) there is a straight line dose-response for DES from the lowest DES dose that has been associated with vaginal adenocarcinoma; (3) the risk of lifetime exposure to DES is identical to the risk of exposure of the child to DES during the mother's pregnancy; and (4) we know the incidence of vaginal adenocarcinoma associated with DES exposure in utero. I will first describe the calculations made from the Herbst data and then elaborate upon my reasons for not accepting the assumptions upon which those calculations are based.

In an article entitled "Environmental Factors in the Origin of Cancer and Estimation of the Possible Hazard to Man" (M–63), the authors, Dr. H. B. Jones and Dr. A. Grendon, calculated that under "very conservative" assumptions the risk of DES-related cancer from meat consumption to the female population of the United States is 3 in 100 million. The authors then assumed that there are 4 million births per year in the United States, so that this risk is equivalent to one cancer every 8 years. Their "conservative" assumptions are as follows:

(1) A pregnant woman eats 10 oz. of beef muscle every day, except 1 day per week, in which 6 oz. of beef liver are substituted.

(2) Beef liver contains DES at a concentration of 2 ppb, and the concentration in beef muscle is 0.2 ppb.

(3) 100 DES-related cancers resulted from pregnant women receiving DES treatment who gave birth during the period 1951–1955.

(4) DES was prescribed for only 1 percent of the 10 million pregnant women during the period 1951–1955.

(5) The dose that elicited the response in each of the 100 cancer victims was 1.5 mg DES/day, the lowest dose administered to pregnant women, as reported to Dr. Herbst in his Registry.

(6) The dose-response relationship to DES is linear in the 0 to 1.5 mg DES/day range. Dr. Jones and Dr. Grendon claim that when they substitute more reasonable assumptions for the six just listed the risk of human cancer in females from the ingestion of DES-treated meat is 2 in 100 trillion (1 trillion=10^{12}), or equivalent to one cancer every 10 million years in the United States. (Id.)

Dr. Thomas H. Jukes, the author of "Diethylstilbestrol in Beef Production: What Is the Risk to Consumers?" (M–104), calculated his risk estimate in a manner similar to that of Dr. Jones and Dr. Grendon. Dr. Jukes assumed a lower daily intake of DES—1.9 nanograms (1 nanogram (ng)=10^{-9} grams=1 billionth of a gram) DES/day as compared to 100 ng DES/day resulting from assumptions (1) and (2) above. Also, in his linear extrapolation from the 1.5 mg DES/day dose level, he assumed that the risk of human cancer pregnant women receiving DES therapy was 4 in 1,000, an upper limit estimate of risk computed by Lanier, et al. (G–44 at 798). Dr. Jukes then arrived at a risk estimate of less than 5 in 1 billion from consumption of DES-treated meat, or approximately 1 cancer every 133 years in the United States (he assumes 1.5 million female births per year in the United States). In his written testimony, Dr. Jukes revises his estimate to 1 case of cancer every 380 to 3,800 years (M–99 at 10), because he substituted for the 4 in 1,000 risk estimate (of cancer to females exposed in utero to DES) the 0.14 to 1.4 in 1,000 estimate proposed by Dr. Herbst (M–26 at 47).

As Bureaus' witness Dr. Hoel stated, "the central assumptions upon which these authors based their calculations have not been validated" (G–55 at 2). My discussion of the four unsupported assumptions made by the manufacturing parties' witnesses that I regard as most important follows:

First, as the Bureaus' Dr. Condon stated, one reason for rejecting these risk calculations is the fact that "they assume that the only type of cancer risk due to DES is vaginal carcinoma because it was the only human cancer on which they based their calculations" (G–21 at 4). See also Dr. Cornfield's statement that "[b]ecause of the lack of studies of other forms of cancer in the women exposed, the human evidence [upon which the manufacturing parties' witnesses rely] cannot be used to estimate a safe dose of DES in food" (G–25 at 2). Particularly in light of the fact that animal carcinogenicity studies show that DES causes cancer in a variety of organs (see, e.g., G–47; G–84), I see no basis for the assumption that DES is associated with only this one rare type of cancer.

A second reason why the risk estimates presented by the manufacturing parties are extremely small is that they have assumed that there exists a dose-response relationship between the incidence of vaginal cancer in females and the dosage of DES administered to their mothers. Put in its simplest terms, a dose response relationship in this context means that an increase in the dosage of DES administred results in an increase in the percentage of persons who are afflicted with cancer. Thus, again to simplify the matter, if cancer were found in 1 in 1,000 persons treated with 1.5 mg of substance X, 1 in 100 persons treated with 15 mg X, and 1 in 10 persons treated with 150 mg X, a dose response would be shown. If that effect were observed, it might be valid to estimate that 0.15 mg X would cause cancer in 1 in 10,000 persons.

Another possibility, however, is that 0.015 mg (or some even lower amount) of substance X causes cancer in 1 in 1,000 persons, and that increases in dosage above that do not add appreciably to that risk. Thus, persons administered 0.015 mg X would be at the same risk as those administered 1.5 mg X or 150 mg X. The assumption that because 1.5 mg X caused one cancer in 1,000, 0.15 mg X would cause 1 cancer in 10,000, would then be incorrect.

The above example oversimplifies this question but does illustrate the problem with the assumption utilized by the manufacturing parties' witnesses. As is often true with retrospective epidemiological studies, it can not be determined from the Herbst data whether there is in fact a dose-response relationship between DES dosage and the cancers observed. As Dr. Condon noted, "no such relationship [between dose and response] has been established" (G–21 at 4). Dr. Hoel reiterated this fact (G–55 at 3):

> There is no scientific support for this assumption. The reported studies of A. L. Herbst, et al. provide no basis for constructing a dose-response relationship for the observed carcinogenic effects. Without such an established relationship, it is not valid to extrapolate these data to low levels of risk.

In general, if no dose-response relationship has been established in the observable dose range, there is no justification for extrapolating to the low dose range via a dose-response curve.

The third unsupported assumption made by the manufacturing parties' witnesses is equally likely to produce a misleading risk assessment. A proper analysis of the risks associated with DES as an animal drug should deal with low-dose, long-term (lifetime) exposure, whereas the women in Herbst's Registry faced high-dose, short-term (during

pregnancy only) exposure to DES. This fact alone invalidates any risk assessment, based on the Herbst data, of human carcinogenesis from consumption of DES-treated meat (see G–21 at 4; G–55 at 3).

A fourth, though less important, unsupported assumption by the witnesses seeking to calculate the risks of DES use is the assumption that the incidence rate of vaginal carcinoma in women exposed to DES in utero is known. As Dr. Condon noted, however, there is a long latent period for vaginal adenocarcinoma; consequently, more cases may occur as the women exposed age (G–21 at 4–5). In addition, there is no certainty that all cases of this type of cancer that resulted from use of DES have been diagnosed and reported to Dr. Herbst.

For the reasons I have discussed, I regard the risk assessments provided by the manufacturing parties to prove the safety of DES in meat as unsupported and unreliable. (Note that, in any case, these estimates say nothing about the risk of cancer posed by DES to the approximately half of the population that is male. I cannot assume, on the basis of the evidence in this record, that DES does not cause cancer in males.)

(ii) *Argument That Approved Uses of DES Present No Risk.* Some witnesses for the manufacturing parties attempted to downplay the risk of DES to humans either because it contributes very little to the total amount of endogenous estrogens or because the amount of DES ingested from meat is well below what are alleged to be no-effect levels.

Dr. Elwood V. Jensen argued that the daily consumption of DES in meat is at most 40 ng and that this amount is insignificant:

> It is my considered opinion that ingestion of 40 or even 400 ng of diethylstilbestrol per day would have no physiological significance in comparison with the 20,000 to 400,000 ng of endogenous estradiol that humans normally produce (in addition to estrone which also makes a contribution to the total estrogen level).

(M–69 at 10). As I have discussed above (section III(D)(1)), however, DES is not an endogenous estrogen, and I cannot find that its carcinogenic and other adverse effects result only from its estrogenic properties.

Dr. Nicholas H. Booth apparently assumed that DES can have no carcinogenic or other adverse effect at a level at which it does not induce a uterine response. He claimed that the no-effect level from the parenteral administration of DES is 0.29 μg/kg body weight (M–40 at 2–4) because (1) the no-effect level from estradiol is 0.166 μg/kg body weight in rats (M–49), and (2) estradiol is 1.72 times more potent than DES in mice when the effect is taken to be an alteration in the vaginal mitotic count (M–48). (The mitotic count is the proportion of cells that are in the process of cell division.) This dosage of DES is 1.5 to 3 times smaller than the 6.25 ppb dosage administered to some of the mice in the Gass study (discussed in section III (D)(2)(a) of this Decision) (M–40 at 40). If beef liver contains DES at 2 ppb, he calculated that the average daily intake of DES from meat is 3.8 ng (twice the amount of Dr. Jukes' estimate), which for a woman weighing 60 kg yields 0.063 ng DES/kg body weight (id. at 6).

Dr. Booth states that if all the DES is absorbed from the gastrointestinal (GI) tract, this amount is 4,523 times below the no-effect level of the rat that he computed (id.). Whereas if only 3 percent of the DES is absorbed from the GI tract, which he regarded as the more realistic situation, this amount (17×10^{-12} g DES/kg body weight) is 167,000 times below Dr. Booth's rat no-effect level (id.).

Dr. Booth also compared (id. at 4–5) the 0.063 mg DES/kg body weight to a no-effect level in humans, which he calculated from a study of the treatment of senile vaginitis with DES (M–50). He estimated the no-effect level for oral administration in humans to be 0.476 μg DES/kg body weight, approximately 1.5 times higher than the parenteral no-effect level in rats (M–40 at 4–5).

It must be remembered what Dr. Booth considered as effects: a uterine response in the rat, a change in the vaginal mitotic count in the rat, and a favorable reaction to the treatment of senile vaginitis in humans. Dr. Booth, in his testimony, did not even discuss his reasons for assuming that these effects correlate with either carcinogenesis or any other adverse effect associated with DES. No evidence in this record demonstrates such a correlation. See the discussion of my reasons for rejecting the argument that DES is no different from endogenous estrogens (section III(D)(1) of this Decision). Finally, the manner in which Dr. Booth combined the results from studies with different species and different methods of administration in order to calculate no-effect levels has not been justified.

I can not agree that any amount of DES, no matter how small, has been shown to be safe. On this point, my conclusion is supported by the opinion of Dr. Rauscher: "Because of the lack of data concerning the exact levels of DES which may elicit cancer in humans, we cannot say how small an amount may cause cancer nor how long that cancer will take to appear" (G–70 at 4). See also Dr. Saffiotti's testimony that "exposure to any amount of a carcinogen, however small, will contribute to the total carcinogenic effect in the population * * *" (G–80 at 6–7).

(iii) *Risk Calculations from Animal Data.* Having found that the risk calculations proffered by the manufacturing parties are invalid, I have considered whether the available data permit any reliable estimate of the risk of DES use. Dr. Hoel noted what he considered to be the only plausible alternative method for conducting a risk assessment of DES in meat (G–55 at 3):

> Estimation of cancer risks due to long-term (lifetime), low-level exposure to DES is, for the present, made only by extrapolation from lifetime toxicity studies in experimental animals.
>
> Even though such estimations require extrapolation from animals to humans, the general absence of risk data on lifetime human exposure to DES makes it necessary to use animal data.

None of the manufacturing parties' witnesses attempted such an extrapolation from animal data.

Some Bureaus' witnesses calculated from the results of the Gass study that 1 ppt DES would present a risk of less than 1 cancer in 1 million exposed (see, e.g., G–34 at 2). This calculation, even if accepted as valid, is hardly relevant to present use of DES which, the record shows, results in DES residues in edible tissues above 1 ppt. (See, generally, section III(B) of this Decision.)

As noted in the section dealing with the analytical methods for DES (II(A)(2)), this calculation is, in any case, unreliable. As discussed in that section, substances metabolize in the body, and the metabolites of a substance may be more toxic than the parent compound. Because different metabolites may be formed by different species (see, e.g., G–24 at 10416), testing of the parent substance in one species can not provide definitive information about the toxicity or carcinogenicity of that substance in other species. If, for example, DES metabolism in the body of a steer produces a carcinogenic metabolite that is not produced by DES metabolism in the mouse, the results of the Gass mouse study would not reflect that metabolite. Thus, extrapolation from the Gass study of DES could show DES to be less carcinogenic to humans than it actually is. Because the required metabolism studies of DES do not appear in the record, there is no basis either for the calculation made by the Bureaus' experts or for any calculation of the risks of present uses of DES.

(iv) *Conclusion as to Quantitative Risk Assessment.* I find that each of the risk calculations for DES proffered by

the manufacturing parties rests on unwarranted assumptions and must be rejected. The record does not provide data that make possible a reasonably well grounded calculation of the risk from the presently approved uses of DES.

(b) *Introduction to Discussion of Benefits.* The discussion that follows deals first with the contention that DES use provides "health benefits" to society by (1) decreasing the amount of fat in the human diet and (2) saving food. I then discuss the evidence in the record that DES use provides an economic benefit to society. Because the argument that one should consider the "health benefits" of an animal drug in determining its safety has some appeal, I have considered the evidence in the record regarding claimed "health benefits" with especially great care. (The manufacturing parties make passing reference to a claimed health benefit from reduction to animal waste (Manufacturing Parties' Exceptions at 178 n. *). Dr. Preston's statement that "there is potentially less animal waste" associated with DES use (M–124 at 4) is all the evidence to which I have been cited on this question and I cannot find, on the basis of that single unsupported statement, that reduction in animal waste is a health benefit associated with the use of DES.)

One factor that the manufacturing parties seem to ignore is the availability of alternatives to DES. If a claimed benefit from the use of DES is also available from a potential substitute, it is appropriate as a matter of common sense and logic to discount that benefit in determining whether the benefits of DES outweigh its risks. (This practice is followed by the Environmental Protection Agency in the risk/benefit decisions it must make, see, e.g., 44 FR 15874, 15876 (March 15, 1979) (2, 4, 5–T); 43 FR 51132, 51135 (November 2, 1978) (endrin).) The proponents of DES have provided very little information to this record about the availability of alternatives to DES.

Information about alternative growth promotants is not readily available from sources of which I could appropriately take official notice. While NADA's approved after 1969 are required to be made the subject of a published regulation, see 21 U.S.C. 360b(i), not all previously approved drugs are the subject of such regulations. Some animal drugs may, in addition, be exempt from the definition of "new animal drugs" or subject to its "grandfather" clauses, see 21 U.S.C. 321(w); Pub. L. No. 90–399, Section 108(3)(1969). Such drugs need not be covered by approved NADA's and thus would not be the subject of published regulations. Even where regulations are published, they show only that a drug is approved. They say nothing about its comparative effectiveness, cost, or availability. The components of the FDA that have first-hand knowledge about animal drugs are, of course, not available to me in making this decision.

The FDA has proposed to withdraw approval of two potential substitutes for DES, Synovex-S and Synovex-H implants, 44 FR 1463 (January 5, 1979). Those products will, of course, be available for some time until withdrawal of their approval is accomplished. Nevertheless, because the FDA is seeking to remove these growth promotants from the market, they will not be considered a factor in the DES benefits determination.

(c) *Health Benefits: Reduction in Fat.* The manufacturing parties and the pro-DES intervenors argued that the ban of DES would actually have adverse health consequences because the edible tissues of animals not fed DES contain more fat than the tissues of DES-treated animals (see Manufacturing Parties' Exceptions at 175–77). As the following discussion illustrates, the manufacturing parties have not supplied to this record sufficient data to make possible any conclusions on this point.

The question whether the ban of DES would result in significant adverse health effects to the public because of an increase in fat in the diet logically must be divided into two questions: (1) How much of a difference in fat in the human diet will cause a difference in the health of consumers? (2) How much difference in the fat consumed by human beings will result from the withdrawal of approval of the DES NADA's?

(i) *Relationship Between Fat Intake and Health.* The manufacturing parties' attempt to answer the first, and simpler, of these questions is unconvincing. They rely soley on the statement of Dr. Jukes (M–99 at 15–16) that a decrease in fat in the diet reduces human exposure to diseases such as cancer, heart disease and diabetes (Manufacturing Parties' Exceptions at 177). Dr. Jukes referred to an article (M–107) that reviews a number of epidemiological reports dealing with various cancers and their possible causes. The thesis of this review is that "over nutrition" is a prominent cause of cancer. The author, Ernest L. Wynder, suggests that the American public should consume a diet lower in calories, total fats, saturated fats, and cholesterol than its present diet. The basis for this recommendation is apparently the differing incidence of breast and colon cancer in various countries. Mr. Wynder did not testify at the hearing and was thus not subjected to cross-examination on his conclusions.

I do not disagree with the general proposition that it would be a good idea for Americans to eat leaner meat, though the record provides little support for that proposition. Nothing in the record, however, provides a basis for determining how much of a fat reduction would make a meaningful difference in the health of consumers. Without *some* basis in the record for a finding on the amount of fat reduction needed to achieve a positive effect on health, I cannot reach any conclusion about the benefit to health from fat reductions attributable to use of DES.

(ii) *Effect of Withdrawal of Approval of the DES NADA's on Fat Consumption.* This question itself involves a large number of subquestions. Logically, the difference in the amount of fat consumed would equal the amount of the difference in fat between the meat of DES-treated animals and the meat of animals that would be marketed after the ban of DES times the amount of beef that would be consumed by human consumers after a ban of DES plus or minus the amount of fat that would be consumed by humans from alternatives to beef or lamb should the ban of DES alter the consumption of those products to any significant degree.

(a) Amount of Fat Saving in Meat. Each of the factors mentioned itself depends on analysis of subfactors. Thus, the amount of the difference in fat between the meat of DES-treated animals and that of animals available to the public after a ban of DES depends on what alternatives there will be to the use of DES. It is, as a practical matter, meaningless to compare the use of DES simply to the production of cattle and sheep without DES. Producers predictably will seek to maximize their profits by turning to alternatives.

The most likely alternative to the use of DES would be the use, in its stead, of alternative growth promotants. The government's environmental impact analysis (G–116) bases its conclusions on the assumption that producers now using DES would switch to other available growth promotants. (Cf. G–115, discussed below.) The environmental impact statement (issued in 1976) assumes the use of the two Synovex products (under their chemical names—estradiol benzoate plus testosterone proprionate and estradiol benzoate plus progesterone), Ralgro by its chemical name (Zeranol), melengestrol acetate (MGA), and monensin.

A large number of alternative growth promotants are mentioned in the record. These include: Synovex-S implant (200 mg progesterone and 20 mg estradiol benzoate) (PS–15, PS–20, PS–25); Synovex-H implant (200 mg testosterone propionate and 20 mg estradiol benzoate) (PS–16, PS–44); Ralgro implant (resorcylic acid lactone), 36 mg (PS–20, PA–25, M–125 at 1419); monensin-sodium (PA–31 at 6); Rumensin (monensin) (an antibiotic) (PA–23 at 453); a feed additive consisting of microencapsulated animal fats (not approved by the FDA as of February 1976) (id.); an intravaginal device to stimulate the expression of estrus in heifers (id.; cf. M–51 at 30); estradiol 17–b (PS–12); melengestrol acetate (MGA) (PS–16, PS–44); dienestrol diacetate (PS–19); hexestrol (dihydrodiethyl-stilbestrol) (id.); coumestrol (an "isoflavonic estrogen" found in alfalfa) (PS–25); zeranol in lambs (metabolic effects) (PS–30); testosterone propionate in lambs (PS–34); chlortetracycline in lambs (id.); reserpine in lambs (id.); Smilagenin (a nonestrogenic substance) (M–125 at 1419). The record does not show that any of the above (other than those products referred to in the environmental impact statement) is or is not now available or likely to be available in the future as an alternative to DES. As discussed above, a notice of opportunity for hearing has issued for withdrawal of approval of both Synovex products (i.e., Synovex-S and Synovex-H).

DES is generally used in the raising of steers (castrated male cattle), which are easier to deal with than bulls and have, in the past, been thought to provide better tasting beef. One alternative to the use of DES is a change in cattle-raising practices. In the European countries in which DES has been banned, meat producers apparently do not castrate bull calves; thus they raise bulls rather than steers (M–64 at 24). The bulls have available, as growth promotants, natural hormones provided by their testes that are comparable to the amount of growth promotant added to steers by the administration of DES (id.). An expert witness for the intervening parties, Dr. Donald R. Gill, stated that his university had produced publications favorable to the raising of bulls (as opposed to steers), but that he personally had had bad experiences with large numbers of bulls fed in commercial feed lots (Tr. at 2006–7). Nevertheless, the raising of bulls is yet another alternative that might be utilized by cattle producers wishing to maximize the growth of their cattle if DES were banned.

The next subquestion is what will be the extent of the difference in fat consumed by the public if DES is replaced by any of the alternative growth promotants. The record has little information on this question. Data on the following alternatives do appear in the record:

No growth promotant at all—Dr. Rodney L. Preston, a manufacturing parties' witness, testified that among the positive effects of the use of DES is the production of meat with more protein and less fat, a result that he characterizes as "in harmony with proper human nutrition" (M–124 at 3). Dr. Preston made no attempt to quantify the increase in protein or reduction in fat to be expected in either cattle or sheep.

A review article by Dr. Preston states that the effect of DES on carcass composition is related to the ratio between dietary protein and dietary energy (apparently, calories). At a certain ratio, DES can be expected, he stated, to decrease the deposit of fat in the carcasses of lambs (M–125 at 1416–17). Again, no amount of decrease is given.

The Administrative Law Judge cited M–109 at 700 for the proposition that the reduction in fat content in treated steers is less than 1 percent (I.D. at 19). He apparently relied upon the estimated fat in total carcass composition reflected on Table 2 of that report. The manufacturing parties take the position, which seems to be reasonable, that the amount of fat in the muscle, as opposed to the total amount of fat in the animal, is important (Manufacturing Parties' Exceptions at 176). They go on to argue that this report, because it shows increased body fat thickness (citing M–109 at 700, 701) and no increase in overall body fat, demonstrated that DES use resulted in decreased intramuscular fat (Manufacturing Parties' Exceptions at 176).

A large number of articles detailing tests with various levels of DES were submitted to the record by the intervening parties (see, e.g., PS–16; PS–17). Review of those articles shows that DES does appear to decrease the fat content of the edible tissues of treated animals, though the amount of decrease varies with the amount of DES used, the form in which it is used, the amount and kind of feed provided to the animals and the age at which they are slaughtered. Because the studies reported involved use of DES under conditions of use different from the approved conditions, it is not possible to determine from these articles how much of a saving of fat in edible tissues occurs when DES is used in accordance with its approved uses.

MGA—DES-treated cattle are reported as having had significantly lower marbling scores than MGA-treated groups (PS–16). (The decrease in fat in the edible tissues of DES-treated animals apparently decreases what is referred to as the "marbling score." The decrease in the marbling score, in turn, decreases the Department of Agriculture grade assigned to the meat products (PS–20 and 1211; see, generally, for present USDA grading regulations, 9 CFR Part 53). Studies relevant to the fat question thus sometime speak of lowered marbling scores or lowered carcass grades.)

Dienestrol diacetate—A 1955 report states that DES-fed steers produced carcasses that were rated under federal carcass grades as slightly inferior to the carcasses from dienestrol-fed steers (and particularly inferior to control animals) (PS–19 at 332–33).

Hexestrol—The same 1955 report found that DES-fed steers produced carcasses slightly inferior in federal carcass grade to the carcasses of hexestrol-fed steers (id.).

Ralgro—One study showed that carcass grades with Ralgro treatment were similar to those resulting from DES treatment (PS–20).

Testosterone propionate—One study showed that DES treatment of lambs caused significantly lower carcass grades than treatment with testosterone propionate (PS–34).

Chlortetracycline plus reserpine—These drugs, when administered together, produced significantly higher grades of carcasses of lambs than did DES treatment (PS–34).

Bulls as alternatives to steers—Bulls are reported as having less marbling in the lean meat than DES-treated steers in one study (PS–4). In another study, bulls were compared with steers in a test in which half of the bulls and half of the steers were treated with DES (24 mg in pellets for the steers and 60 mg in pellets for the bulls). The report states that the carcasses of both the treated and the untreated steers were significantly higher in fat content than the carcasses of the untreated bulls (PS–35). A table in the study shows that the carcass grades of the treated steers were higher than the carcass grades of the untreated bulls and that the percentage of carcass fat in the treated steers was greater than the percentage of fat in the treated bulls (id. at Table 3). A subsequent evaluation of animals from this study also found that steers generally had more abundant marbling than did bulls (PS–36).

None of the cited information gives a real basis for a calculation of how much, if any, saving in the fat content of meat would result from the continued use of