ITER Peer Review Meeting Summary

July 26, 2000
Teleconference

An independent panel of expert scientists, including risk assessors, met in a teleconference to review a revised risk assessment on the lifetime skin cancer risk from the use of coal tar containing shampoos. The same panel met on June 5 and 6 in Cincinnati to discuss the original assessment. At that time the panel offered the authors, the K.S. Crump Group, Inc. of ICF Consulting, a number of recommendations for revision and improvement (June 5 and 6, 2000 meeting summary). The purpose of this conference call meeting was for the panel to review the revised document. ICF wrote the assessment for American Home Products in order to provide that company with information related to the need for consumer labeling of shampoos under California's Proposition 65. The Neutrogena Company was also a co-sponsor of this peer review.

This peer review meeting was conducted by Toxicology Excellence for Risk Assessment (*TERA*); a non-profit organization dedicated to the best use of toxicity data in risk assessment. Expert peer reviewers donated their time and talents to provide an independent review of the assessment. The objective was a comprehensive overall review of the materials as provided by the combined experience of all the reviewers. This meeting summary represents the major discussions and conclusions of the panel as a whole and is the official record of the conference call.

After brief introductory remarks, the meeting began with an update to the previous meeting's discussion of conflict of interest. Prior to the June meeting, each reviewer had certified in writing that he or she did not have a conflict (real or apparent) with the chemicals under review or with the sponsors (identified to the reviewers before the meeting), or identified the potential for such conflicts. At the June meeting the panel discussed conflict of interest and reached agreement on each person's participation; the panel's decision is reflected in that meeting's summary. At that time the panel had discussed possible appearance of conflicts for Drs. Roy and Finley and unanimously agreed that they should participate fully in the discussion and be polled for consensus. However, all panel members were asked to look for undue influence on the discussions, and any panel member was given the ability to approach the Chair to state an issue of undue influence. The Chair would then decide whether additional panel discussion would be needed.

Dr. Parkin asked to update her statement. She indicated that following the June meeting, she was performing her annual review of her stock portfolio and became aware of the fact that she owned a number of shares of Johnson and Johnson stock. She was not aware of this at the last meeting and indicated that she believed it was not a conflict of interest. The panel unanimously decided that Dr. Parkin's situation represented a possible appearance of a conflict and she should participate in the discussion and be polled for consensus. However, as with Drs. Roy and Finley, any member of the panel was encouraged to indicate to the Chair if they believed that Dr. Parkin was exhibiting bias at which time the Chair could decide to reopen the conflict of interest

discussion (the conference call was arranged so that individual panel members could signal the Chair privately).

Dr. Finley also asked to update his statement. He indicated that on July 25, 2000, he became aware of the fact that another member of his firm had recently been retained by a coal tar manufacturer. Dr. Finley did not believe that this was a conflict because he had already completed his review and formed his opinion of the risk assessment before he learned of the situation. The panel unanimously decided that Dr. Finley's situation represented an appearance of a conflict and that he should participate in the discussion, but not be polled for consensus.

Full discussion and participation were encouraged during the conference call and agreement was reached by consensus. Consensus for the purpose of these meetings is defined as "an opinion held by all or most, or general agreement." The meeting was open to the public and individuals from Orrick, Herrington & Sutcliff, LLP; Gradient Corporation; Occupational Knowledge International; and, Preston Gates Ellis LLP listened to the proceedings.

At the start of the meeting one of the observers, Mr. Perry Gottesfeld of Occupational Knowledge International and a co-litigant with the State of California on the Proposition 65 lawsuit, announced that he intended to tape record the call. Ms. Jacqueline Patterson of *TERA* then asked for a sub-conference where Dr. Dourson explained to Mr. Gottesfeld that taping the meeting was contrary to *TERA's* observer policy. This is because creating tapes -- for purposes other than helping with writing the official meeting notes and where the tapes are subsequently destroyed -- allows the identification of individual comments. In *TERA*'s experience, such identification may inhibit the free flow of discussion amongst panel members because comments can be taken out of context. This inhibition would not necessarily be in the best interests of protecting the public health. After the sub-conference, the Chair polled the panel for their opinion on recording the meeting. The Chair abstained; the remaining panel members indicated that the meeting should not be recorded. Mr. Gottesfeld then asked to make a comment to the panel, which the Chair allowed. After the comment, the Chair again polled the panel for their opinion on recording the meeting. The second vote was the same as the first. The Chair then informed Mr. Gottesfeld that he did not have the consent of either *TERA* or the panel to record the call, and asked him to stop his recording from that point on.

Estimation of Lifetime Skin Cancer Risk from the use of Coal Tar Containing Shampoos Follow-up Review

Sponsor: Orrick, Herrington & Sutcliff, LLP on behalf of American Home Products, and the Neutrogena Corporation

Presenters: Mr. Bruce Allen, ICF Consulting, The K.S. Crump Group, Inc.
Dr. Annette Shipp, ICF Consulting, The K.S. Crump Group, Inc.
Ms. Robinan Gentry, ICF Consulting, The K.S. Crump Group, Inc.

Chair: Dr. Michael L. Dourson, *TERA*

Review Panel:

In Attendance:

Dr. Michael L. Dourson, Toxicology Excellence for Risk Assessment
Dr. Brent Finley, Exponent
Dr. Loren Lund, Parsons Engineering Science, Inc.
Dr. Brian Magee, Ogden Environmental & Energy Services
Dr. Rebecca Parkin, George Washington University, Department of Environmental and Occupational Health
Dr. Tim Roy, Petrotec
Dr. Ted Simon, U.S. Environmental Protection Agency, Region 4
Dr. Allan Susten, Agency for Toxic Substances and Disease Registry, Division of Health Assessment and Consultation
*Dr. Glenn Talaska, University of Cincinnati, Department of Environmental Health
Dr. Rebecca Tominack, Missouri Regional Poison Center

*Dr. Talaska had to temporarily leave the conference call and did not take part in the polling for consensus on sections 2B, 3A/B, 3C/D/E, and 4.

Could not attend:

Dr. Brian Adams, University of Cincinnati, College of Medicine
Dr. John Gamble, Exxon Mobil Biomedical Sciences, Inc.
* Dr. Alan Stern, New Jersey Dept. of Environmental Protection

*Provided written comments, which were read into the meeting by the Chair or discussed by other panel members:

The authors briefly summarized some of the major revisions they had made and responses to the panel's recommendations and suggestions from the June 5 and 6 meeting. The panel discussed the revisions made to the ICF assessment in a number of areas, including:

- Estimation of the No Significant Risk Level (NSRL) using the Pittelkow et al. (1981) study

- Sensitivity and uncertainty analyses
- Estimates of exposure for shampoo users
- Issues related to children
- Use and analysis of animal data.

A complete summary of revisions made to the assessment is contained in the attached "Disposition of Comments" document prepared by ICF (see Attachment A). The panel reviewed this document, along with the revised assessment, in preparation for the July 26 conference call. The following text summarizes the highlights of the discussion, which focused on the major revisions made to the assessment.

1. Estimation of the NSRL using the Pittelkow et al. (1981) Study

Author Presentation and Clarifying Questions

Mr. Bruce Allen of ICF Consulting briefly highlighted four significant changes they have made to the assessment in this area. First, they incorporated uncertainty regarding expected incidence rates into the main analysis (Section 3 of the assessment). Second, the lifetable analysis was extended to include from birth to age 70 years and dose-response and exposure assessments are now consistent in this regard. Third, the estimation of the NSRL is now based on absorbed dose, rather than the applied dose. The authors used data from a study by Santella et al. (1994) which measured excretion of 1-hydroxypyrene (1-OHP), a metabolite of pyrene, in psoriasis patients treated with coal tar ointments. Fourth, the average years of follow-up for persons who died during the follow-up years was estimated to be 13 years based on the total years of follow-up. For the persons who did not have cancer, the median value of the distribution used was 14. Consequently, those individuals who died during follow-up years would appear to have had years of follow-up (treatment) that corresponds well with the assumed distribution.

A reviewer asked whether the authors used the same fraction absorbed for estimating dose for the NSRL calculation and the shampoo exposure assessment. An author responded that the same approach was used for both; however, the data differed to reflect the different exposure condition or mode of application [ointment (Santella) vs. shampoo (Van Schooten)]. Another reviewer asked whether the authors had adjusted for the volume of skin covered in both situations. The author indicated that they had not done this explicitly; they assumed that 1-OHP in urine reflected the amount applied that was absorbed.

Another reviewer noted that the distribution of fraction absorbed appears truncated in the figure on pages B9-B10 of the document, and asked how the authors estimated the bounds for this parameter. The author explained that the truncation is an artifact of the graphing program; the distribution included values below 19%.

A reviewer asked for clarification on how the authors added additional distributions into the main analysis. The author noted that distributions to account for the uncertainty around the expected incidence rates were added to the main analysis. For the observed incidence, the best estimate was 19/260, but this was allowed to vary in each iteration in order to account for uncertainty in sampling from the Poisson distribution.

Another reviewer asked for clarification regarding the means and medians in the distribution for years of at home use. The author indicated that a triangular distribution was used with a minimum of four, a maximum of 27, and a most likely value of 26.

Panel Discussion

The panel discussed the estimation of the NSRL as five separate topics.

A. Distributions for observed and expected incidence rates
B. Other revised parameters
C. NSRL expressed as absorbed dose
D. Other issues
E. Estimation of the NSRL

1. A. Distributions for Observed and Expected Incidence Rates

A panel member commented that the revisions made in this area were responsive to the panel's concerns and the reviewer provided comments on a few issues. On the issue of the potential for over- and under-reporting of skin cancer, the reviewer made a number of comments. The papers by Scotto on incidence of skin cancer reporting were designed to examine under- and over-reporting and this should be explicitly mentioned in the text to strengthen the discussion. Similarly, the U.S. Department of Health and Human Services (1989) data should be better explained. This reviewer thought the papers on under- and over-reporting of cancers other than skin cancer do not belong in the discussion, as they do not directly apply to skin cancer. Another reviewer thought they should be included to show that the authors have reviewed the literature, but it should be noted that these data are not informative. The first reviewer thought that the Scotto papers were looking at patients who were coming in for routine visits and asked the authors to confirm this as the patients responses might offer a different perspective if this is the case. The first reviewer also asked that the authors clarify the selection of an assumption of 10 percent more or less observed cases used in the uncertainty analysis, given the calculation of 14% over-reporting. An author indicated that they can search for more literature on over- and under-reporting and can add more explanation as suggested.

With regard to the issue of Pittlekow patients lost to follow up or those who did not respond to questions, the first reviewer noted that information about patients might be missing for various reasons. Although a second reviewer pointed out, and the first reviewer agreed, that losing 20 persons in a cohort of 280 is acceptable for 25 years post treatment, the issue of information missing for about half of the patients for questions key to this risk assessment (e.g., sunbelt residency) remains a concern to the first reviewer. Pittlekow et al. do not explain the reasons for the decreased response rates for specific questions, so it is not possible to know why information is missing or what type of uncertainty may have been introduced in the assessment because of the missing information. If the authors are able to interact with Dr. Pittlekow, it would be valuable to learn the reasons why response rates were so low for specific questions.

A reviewer suggested softening the sentence on page 5-11 of the revised document which states that "…the essentially negative epidemiological data…very nearly indicates that there is no risk whatsoever…" as the reader can see this without such an emphatic statement. Another reviewer added to this suggestion by asking that all definitive statements regarding the negative findings of clinical epidemiology studies in chapters 3 and 5 be mollified.

A reviewer noted that the approach used in the sensitivity analysis in the observed and expected responses was reasonable, but that confidence statements should be lessened somewhat because the analysis resulted in different NSRL values. This reviewer also suggested that only one digit of precision be used for the NSRL.

The panel reached unanimous consensus that the treatment of the observed and expected incidence is adequate and appropriate and revisions should be made to the document to clarify the following points:

- In the discussion of the potential for under- and over-reporting of cancer, either delete the reference to other types of cancer or explain that the other types are not informative for skin cancer reporting.
- Add explanation of purpose of the Scotto papers.
- Revise strong definitive statements that coal tar shampoos are not carcinogenic in Sections 3 and 5.
- Ask Dr. Pittelkow how people were lost of follow up (it is not expected that the answer to this question will change the quantitative estimate, but if it does, inform the panel). Also ask Dr. Pittlekow why certain questions were not answered.
- Precision should be one significant digit wherever appropriate.
- Explain basis for selection of variation of 10% for observed incidence used in the sensitivity analysis.

1. B. Other Revised Parameters

One reviewer commented that by changing the number in the cohort from 280 to 260, the document appropriately handled the people lost to follow up. The revisions made to the lifetable analysis were appropriate, as were the revisions made to the estimation of days of home treatment. This reviewer was still not sure that the days of hospital treatment were estimated appropriately, as the reviewer was not convinced that there was a maximum of two hospital treatments in the Pittlekow cohort. Other studies of psoriasis patients indicate that psoriasis patients may undergo multiple Goeckerman treatments. The reviewer suggested that the authors might quantify the exposure from additional hospital visits using the data on percentages of patients with more than two visits from other studies (e.g. Muller and Perry, 1984 study of the Mayo Clinic). Other reviewers noted that even if the exposure of people who may have had more than two hospital visits was not included in the estimate of dose, this omission would only serve to make the risk assessment more health protective, because including them would increase the NSRL. The authors indicated that they felt their upper limit on the distribution for this parameter might be too low, given the lack of information on number of visits. However, they felt that they did not miss any exposure to the cohort because they included the median number of days of hospital treatment; it did not matter how many visits these days were divided into.

The panel reached consensus that overall the approach taken by the authors in revising the parameters discussed above was appropriate. The document should be revised to describe the effect of not considering people in the cohort who may have had more than two clinic visits. Specifically, the text should indicate that not including this potential exposure tends to make the risk assessment more protective. The authors might revise the upper limit of the distribution for this parameter to try to account for this exposure if they wish. The panel suggested that if the authors decided to revise the upper bound, they should consult with the specific reviewers who made suggestions at the meeting.

1. C. NSRL Expressed as Absorbed Dose

Overall, the panel approved of the revised approach to estimate the NSRL based on an absorbed dose rather than an applied dose. One reviewer suggested that two additional studies be included in the document. The first was a study by Van Rooij et al. (1993) that used coal tar ointment and measured 1-hydroxypyrene (1-OHP) excretion. This paper reported absorption data that was at the low end of the distribution used by ICF and the reviewer suggested that if the distribution is not truncated then the text should at least discuss this information. This reviewer also suggested that the loading rate in the Santella (1994) study of 1-5 mg ointment/cm^2 is similar, but slightly less than the loading rate of 9 mg/cm^2 that is used in the risk assessment. An author noted that the Santella study measured excretion over 24 hours after ointment had been applied for 3 days. A steady state is assumed and the measurement would represent all possible excretion.

Another reviewer asked whether the distributions for P_a and P_e (two of the factors that comprise the fraction absorbed parameter) should be correlated in the Monte Carlo analysis, given the assumption that they are linked. This reviewer also questioned the widely disparate values reported for C_f of 3% and 81%. An author indicated that they were only trying to estimate fraction of applied amount that was absorbed. They used the 1-OHP value in urine and assumed a similar shaped distribution for the pyrene applied.

Another reviewer questioned the use of 1-OHP excretion as a surrogate for absorbed dose. This reviewer indicated that 1-OHP indicates systemic absorption, not an estimate of the amount of coal tar constituents retained in the skin. This reviewer asked if 1-OHP was correlated with DNA adducts in the skin. The reviewer noted a paper by Storer et al. (1984) where the authors applied 2% coal tar ointment and measured PAH in blood of volunteers. In spite of the presence of BaP (220 ppm), benzo(a)anthracene (560 ppm), and benzofluoranthene (420 ppm) in the coal tar mixtures, these compounds were not detected in blood of the volunteers. The compounds that were detected in blood (e.g., phenanthrene, pyrene, anthracene, and fluoranthene were the more soluble compounds and had toxic equivalency factors (as compared to BaP) ranging from 0.01 - 0.001 (most were 0.001). Thus, pyrene in urine may not be a good indicator of "absorption" of the more active PAHs; however, it is a good indicator of exposure to coal tar products and sources. The reviewer also discussed the paper by Godschalk et al. (1998) which measured DNA adducts in the skin and tried to correlate 1-OHP and 3-OHP with DNA adducts. The reviewer indicated that absorbed dose is better measured by an endpoint in the skin, rather than a urinary measurement of 1-OHP, but acknowledged that such a skin endpoint was still needed. The reviewer suggested that the Godschalk paper should be included in order to correlate urinary

excretion of PAH metabolites present in the urine with DNA adducts in skin. The Godschalk paper found no correlation between excretion of 1-OHP and total DNA adducts. 3-Hydroxybenzo(a)pyrene excretion, but not that of 1-hydroxypyrene, correlated significantly with the levels of DNA adducts in skin that comigrated with benzo(a)pyrene-diol-epoxide-DNA. Another reviewer agreed and noted that Godschalk found adduct levels in skin that were significantly higher than what was seen in blood lymphocytes. Other reviewers indicated comfort with the use of 1-OHP excretion as a surrogate for skin penetration, as this type of surrogate is what is used in medical practice.

Other reviewers questioned how well 1-OHP excretion represented the absorption of the other PAH constituents of coal tar, given that the skin is a potential reservoir for PAHs. One reviewer noted that the assessment assumes that 26% of the coal constituents are absorbed in skin as a reservoir and that the active constituents, such as BaP, are actually taken up less than pyrene, the parent of 1-OHP. Therefore, increasing the fraction absorbed will actually make the risk assessment less conservative (i.e., less health protective). A reviewer also noted, however, that the amount of 1-OHP in urine following exposure to shampoo is very small compared to the amount following exposure to ointment. However, use of 1-OHP accurately reflects the relative amount of absorption between ointment and shampoo users, which is the key issue of interest.

Another reviewer asked if it was possible to quantify the ratios of 1-OHP to other carcinogenic PAHs. The reviewer also suggested that even if it were not possible to quantify these ratios, the document should include a qualitative discussion of the relative differences in absorption between the different PAHs in a coal tar mixture. The document should also indicate that 1-OHP may not be representative of the absorption rate of active PAHs.

The panel reached unanimous consensus that use of absorbed dose is the appropriate approach to estimating the NSRL because it allows evaluation of the ratio of absorption between users of coal tar ointments and coal tar shampoos. Use of 1-OHP is the appropriate dose metric for absorption of PAHs from coal tar products and that cancer is the endpoint of concern. The text should be revised to enhance the discussion in three areas: the differences in potential absorption between ointment and shampoo use; the relative dermal penetration of pyrene, as measured by 1-OHP, compared to the active PAHs in coal tar shampoos; and the correlation of urinary excretion of PAH metabolites with DNA adduct formation in the skin.

1. D. Other Issues

Other issues identified by the panel at the June meeting, and under consideration for estimating the NSRL included the incorporation of information on prior coal tar treatment in the Pittelkow cohort, the gender proportions in the cohort, the issue of shampooing in the cohort, the average years of follow up for the cohort members who died, the ratio of squamous cell carcinoma to basal cell carcinoma, the comparison of psoriatic to normal skin, the use of occupational data, and the question of systemic tumors. One reviewer thought that these issues were appropriately handled in the document, with the exception of a discussion of gender proportion for the Pittelkow cohort, which the reviewer could not find. The authors noted that according to the sensitivity analysis, gender is an insensitive parameter, so acquiring data on the proportions of males and females would not affect the outcome of the risk assessment. Other reviewers agreed

with the first reviewer's summary and several also indicated that the comparison of psoriatic and normal skin that was added to the revised document was well done. One reviewer questioned whether average lifespan could be equated to coal tar use for assessing the average years of follow up for the cohort members who died. However, this reviewer also noted that choosing a different approach would not likely change the risk assessment. The reviewers asked whether the authors had been successful in contacting Dr. Pittelkow to find out answers to several questions including the amount of prior coal tar treatment in cohort, the use of shampooing in the cohort, and the SCC/BCC ratio. The authors indicated that they had contacted Dr. Pittelkow and that he was getting clearance to answer their questions.

The panel reached unanimous consensus that the assessment's treatment of the issues discussed in this section was adequate and appropriate. The authors should follow up with Dr. Pittlekow for any further clarification on the following issues: any prior coal tar treatment in the cohort, the use of coal tar shampooing during the Goeckerman treatment for cohort members, the ratio of squamous cell carcinomas to basal cell carcinomas in the cohort.

1. E. Overall Agreement with NSRL

The panel reached consensus on the estimation of the NSRL based on the Pittelkow study, assuming that the authors are responsive to the issues and recommendations made in previous discussions. One member abstained; stating that the question was outside that individual's area of expertise.

2. Sensitivity and Uncertainty Analyses

The panel discussed the sensitivity analysis and the use of alternative assumptions for the uncertainty analysis separately.

2. A. Sensitivity Analysis

One reviewer indicated that the summary of the distribution of regions of residence for the skin cancer cases should acknowledge that there is uncertainty in the time of residency relative to the diagnosis and/or onset of the cancers. This reviewer also commented that the normal distribution used to represent the time post-treatment spent in the sunbelt region of the country ignores the uncertainty about the assignment of cases to regions of the country. It is not known whether the time of residency in the various regions refers to the time immediately following treatment or the time of diagnosis, and therefore, it is not known to what extent this assignment should reflect the background skin cancer risk in any case. An author indicated that they do not have information on the timing of residence and timing of skin cancer diagnosis, and so assume it is random or that the information is representative across places of residence during time before skin cancer diagnosis. They might discuss this qualitatively in the text.

The same reviewer also questioned the assignment of the lowest subjective degree of uncertainty to the assignment of the cases with unknown home treatment. (Note -- the authors indicated that cases with unknown treatment were found in both the group with cancer and the group without cancer.) If there is no basis for estimating or deducing the extent of home treatment for these

cases, then the reviewer asked the authors to explain the basis for asserting that there is little uncertainty associated with this variable. This reviewer had difficulty believing that the assignment of unknowns to treatment groups makes less than a 7.5% change in the outcome when the unknowns are 16% of the cancer cases (3/19). Another reviewer also agreed that the assignment of unknowns should be clarified. This reviewer felt that the unknowns should be assigned based on the severity of their skin condition. The authors agreed that if data were available on the severity of the disease, that these data would be the best approach for assigning unknowns. However, data on severity are not available. The authors indicated that the distributions on the unknowns indicate that if all individuals are allocated equally to treatment groups, there is less than 7.5% change in the potency, compared to the case where each is assigned based on the pattern of those with known use patterns.

Another reviewer noted that the qualitative discussion of the sensitivity analyses were straightforward and easy to understand.

The panel reached unanimous consensus that the sensitivity analysis presented in the document is adequate and appropriate. The text should be revised to provide additional qualitative discussion on the following issues: the effect of uncertainty in the residency time in different regions on the analysis of expected incidence and relative risk; uncertainty about the assignment of cases to regions of the country for estimation of expected incidence; and assignment of cases with unknown home treatment to appropriate groups for estimation of dose.

2. B. Analyses Using Alternative Assumptions

The uncertainty analyses considered different underlying distributions for: the observed and expected incidence rates; the assignment of the unknowns; the fraction of the body treated at home; the days of home treatment greater than 50; the alternative distribution of expected incidence rates; the alternative distribution for percentage coal tar used at home; and, the alternative distribution for the amount absorbed. The panel discussed these items (except discussion of observed and expected incidence rates, which was included with issue 1.A.). Several reviewers commented that the discussion of the sensitivity and uncertainty analyses was greatly improved in the revised document.

Several reviewers questioned why the document included the uncertainty associated with the expected incidence in the main analysis but included the uncertainty associated with the observed rates in the uncertainty analysis. The authors indicated that the main analysis included uncertainty about the three primary inputs: dose, observed incidence rate, and expected incidence rate. For the observed rate, the main analysis assumed the best estimate was 19/260, but that this value was allowed to vary in each iteration to account for uncertainty in sampling from the Poisson distribution. In the uncertainty analysis, the distributions were altered to account for the uncertainty associated with over- or under-reporting of incidence (i.e., something other than 19). For the expected incidence, the uncertainty analysis used the same range of rates, but assumed a triangular distribution.

A reviewer agreed with the use of 10% more or 10% less observed incidence in the uncertainty analysis, but thought the confidence in the NSRL should be medium to high (rather than high), because the NSRL does change with the alternative observed incidences.

One reviewer asked about the alternative distribution for the days of home treatment greater than 50 and why an alternative of 3 days/week was not used. An author indicated that in the main analysis they have assumed a uniform distribution of 51-365 days with a median and mean of 208 days (which is equal to four days/week). The reviewer thought that a certain number of times per week is more reflective of human nature. The authors indicated that they did include a qualitative discussion of a different number of days per week, but did not provide a quantitative analysis for this or put a higher probability on once or twice per week. The author suggested and the reviewer agreed that this might be something to discuss with Dr. Pittlekow. The panel did not have comments on the other issues under consideration.

The panel reached unanimous consensus that the alternative assumptions and distributions presented in the document were adequate and appropriate for evaluating the uncertainty in the risk assessment with an expansion of the explanation for the greater than 50 days parameter. The alternative assumptions made regarding observed and expected incidence from Pittlekow et al. were discussed as part of the estimation of the NSRL (see 1.A.).

The panel also agreed that, overall, the sensitivity and uncertainty analysis were well done, assuming that the authors are responsive to previously raised issues and recommendations. One panel member abstained, stating that this question was outside that reviewer's area of expertise.

3. Issues Related to Estimates of Exposure for Shampoo Users

Author Presentation and Clarifying Questions

Mr. Bruce Allen of ICF Consulting briefly highlighted the major changes in this area. For estimation of ounces of coal tar shampoo used each year, the authors relied solely upon the Neilsen data and used data for all coal tar shampoos rather than a single product. For estimation of years of use, they used the Toppmeyer information on years suffering from scalp condition and age; this distribution included 70 years. For absorbed dose they used a distribution based on the data from Van Schooten et al. (1994) for characterization of typical use. There were no clarifying questions.

Panel Discussion

The panel discussed issues related to the exposure estimates in two groups:

- Shampoo usage per year and years of exposure (shampoo use)
- Estimates of absorbed dose and typical intake, the effect of different coal tar mixtures and shampoo formulations, and the estimate of 102 ounces per year from a European Union (EU) document.

3. A. and 3. B. Shampoo Usage per Year and Years of Exposure

One reviewer commented that the use of the Nielsen data were appropriate as a source of the estimate of ounces shampoo used per year because these data represent actual purchased product from a large number of households. However, the document needs to explicitly state that this represents all coal tar shampoos, not just one specific product. The reviewer also agreed with using the number of years of having skin disease, obtained from Toppmeyer, as a surrogate for the years of exposure. The reviewer acknowledged that the Toppmeyer data alone is weak, but that the "reality check" using the Pittelkow data in the document showed a fairly good correlation. The use of one to 70 years is appropriate. The reviewer asked if there were any demographic data in the Nielsen study that described who was purchasing these products. The authors replied that Nielsen did not contain this type of data. The panel had no additional comments on these issues.

The panel reached unanimous consensus that the approach taken by the document in estimating these two parameters was adequate and appropriate. No additional revisions were recommended.

3.C., 3.D., and 3.E. Estimates of Absorbed Dose and Typical Intake, Coal Tar Mixtures, Shampoo Formulation, and 102 oz/year

Two reviewers indicated that the argument for applying the median exposure from shampooing rather than the mean exposure is based on the interpretation of the term "typical". This argument is really more of a legal-semantic issue than a scientific issue; a case could also be made for the use of the mean value. One reviewer suggested that both the mean and median be presented in the document. Another reviewer favored the median because the data are skewed and the median would be more representative of the average exposure.

Several reviewers suggested that the document needs to include additional discussion regarding coal tar components and what the specific mixtures might include. Another reviewer suggested that the document should include a discussion of the different shampoo formulations and how different formulations may affect assumptions made regarding action of the active constituents. This reviewer did not think the formulations (e.g., inclusion of surfactants and alcohol) would effect the result much however, due to the immense water load in shampooing, but felt it should be described qualitatively. A reviewer noted that the Van Schooten et al. (1994) paper indicated that it had selected a shampoo with the highest PAH content to study. This reviewer noted that the document should indicate whether this shampoo is available in California or is typical of shampoos used in California. An author confirmed that what was used was a product that corresponds to a typical American product. The reviewer asked that this information be added to the document. An author agreed that they could enhance the discussion of the coal tar mixtures and components of the shampoos. The author noted that pharmaceutical grade coal tar could have various formulations and can have different absorption properties. This would seem like the minor difference, rather than order of magnitude range of differences in constituents. The authors expected that the range of absorption would encompass these differences.

Another reviewer asked about the estimate of 102 ounces shampoo used per year cited in an EU document. The authors indicated that the value of 102 ounces was used in an EU document to represent all shampoos used (not just coal tar shampoos) and that the EU document further assumed that only 10% of this shampoo came in contact with the scalp, leaving the remainder unavailable for absorption. They also assumed that only 1% remains as a residue. With these assumptions, the resulting estimate of exposure (~ 10 ounces/year) is very similar to the estimate of ounces of shampoo obtained from the Nielsen data; moreover, the distribution used in the ICF risk assessment also goes beyond 10 ounces/year.

The panel reached unanimous consensus that the quantitative approach used in the document to address these parameters was adequate and appropriate. However, the document should be revised in the following manner: enhance the text on the mixtures issue; add information on the different types of shampoo formulations; add text that the shampoos used in the Van Schooten et al. (1994) study are typical of coal tar shampoos for sale in California; and contrast the use of the mean with the use of the median, perhaps including both values. In addition, the panel reached unanimous consensus that it agreed overall with the Exposure Assessment, including the enhancements as discussed above.

4. Issues Related to Children

The authors did not make a separate presentation for this issue.

Panel Discussion

The panel discussed several issues related to children's risk including the lifetable analysis, the potential increase in the sensitivity of child's skin to constituents in coal tar, and the potential increase in the total lifetime exposure by considering exposure during childhood. A reviewer noted that the risk to children was handled appropriately in the lifetable analysis and that the discussions on absorptive capacity and differences in children and adult skin were very good. Another reviewer noted that the issues raised at the June meeting had been addressed adequately and nothing further needed to be added or enhanced. The panel unanimously agreed that the assessment adequately addressed the issues related to children's exposure.

5. Use and Analysis of Animal Data

Author Presentation and Clarifying Questions

Ms. Robinan Gentry of ICF Consulting briefly highlighted the major revisions to the assessment for the animal analysis.

- The quantitative analysis was moved to an appendix (a footnote in Section 3 referring the reader to the appendix was left off by mistake).
- An uncertainty analysis was added to give a sense of the bounds. A multistage model was used rather than time-to-tumor since the multistage model fits better with a Monte Carlo analysis.
- The absorbed dose was calculated so that it could be compared to the NSRL.

- ICF reviewed the data used for the point estimates and developed distributions for the Monte Carlo analysis. The mouse value (50%) based on absorbed dose was 58.5 and it varied by a factor of six for the 5^{th} and 95^{th} percentiles.

There were no clarifying questions.

Panel Discussion

The panel discussed several issues related to the use and analysis of the animal data including the revisions made to the main text regarding the animal data, the appropriateness of the appendix containing the mouse NSRL, the estimation of uncertainty in the mouse NSRL, the mode of action, the variability in the response of different mouse strains, and the differences in promotional mechanisms between human and mouse.

One reviewer summarized four issues with the animal analysis. First, the reviewer noted that the document was generally responsive to the suggestions and recommendations made by the peer reviewers at the last meeting. The analysis of the animal data has been moved to an appendix, an uncertainty analysis has been added, and the distributions have been expressed as absorbed dose to facilitate comparison with the human NSRL. The reviewer suggested that the main text should be revised to refer readers to the appendix and to provide context for the animal assessment, and provide an explanation of why the appendix was included. Since the assessment contains statements that it is not appropriate to do a quantitative analysis based on the animal data, a better explanation is needed as to how the quantitative analysis fits with the purpose of the assessment document.

Second, the reviewer noted that the absorbed fraction in animals was based on *in vitro* data in animals, but on *in vivo* data for humans. However, *in vitro* data are available for humans in the Storm et al. (1990) study. In addition, the assessment uses distributions to estimate the fraction absorbed in animals, but did not use distributions for the same estimate in humans. An author noted that when they attempted to get a point estimate for each value used in calculating the fraction absorbed, the fraction in humans most representative for shampoo exposure was based on the Van Schooten data, although they also considered the Storm data. The authors also noted that no adjustment for human absorption was necessary with the Monte Carlo analysis, because the NSRL was to be estimated as an absorbed dose. A human absorption fraction would only be needed to estimate an applied amount.

Third, the panel had asked that the authors attempt to bound the estimates for volume of skin and skin thickness. A rationale and additional discussion regarding the selected bounds for the estimated volume of skin in the mouse are needed. An author noted that they did not have data on the variability for this parameter, but could look further to provide a better justification for their selection.

Fourth, the document indicates that the reason the animal data should not be used to develop a NSRL is that the studies use creosote rather than coal tar products. The reviewer acknowledged that it is valid to argue that the mixture is different and not reliable for quantitative estimates for pharmaceutical coal tar exposure to humans. But the reviewer pointed out, there are some

significant dynamic differences between mouse and human skin that lead one to question the usefulness of mouse skin painting studies for human risk assessment and would prevent the use of any mouse skin painting studies for risk quantification. Another reviewer agreed and noted that given the weight of evidence for the epidemiological data and specificity of the material, one mouse skin study with a test material that is so far from shampoo may be irrelevant. This reviewer thought that the paucity of data on the material of interest should convince one not to go forward.

Another reviewer suggested that the Godschalk et al. (1998) paper, which examined DNA adducts in skin, should be discussed in the appendix and may provide insight between the human and mouse. The authors indicated that they would include this paper, but that DNA adduct formation is not the key difference in response between human and animal skin.

The reviewers discussed whether an animal NSRL should be included in the document at all. A reviewer noted that if one were to attempt a quantitative risk assessment with these animal data, then the authors have done an admirable job addressing pharmacokinetic differences and the discussion is informative and useful. It was enlightening for that reviewer to review the analysis that included the kinetic differences and see how the results were very different. However, the primary choice should be use of the epidemiology data. Another reviewer indicated that an NSRL based on mouse skin is not appropriate, should not be done, and that including the appendix sets an inappropriate precedent. Other reviewers suggested that since other groups have already attempted an animal NSRL, the precedent has already been set, and including the appendix provides additional frame of reference for the human NSRL. An author noted that in developing this assessment, the authors became convinced that the mouse skin painting could not be used and decided not to use it. They included it because they thought people would ask, "what if you did?" However, they feel very strongly that the mouse data should not be used quantitatively.

The panel reached consensus that an appendix with the mouse NSRL should be included in the document. The sole abstaining member did so due to concern over the precedent it would set for using mouse skin painting studies for human risk assessment. The Chair indicated that the authors should also add a discussion in the body of the text that provides a better link to the appendix and to adjust the text on page 2-16 of the document to reflect the panel discussion.

6. Other Issues and Comments

The panel reached unanimous consensus that if the authors and sponsors wished, this assessment can be loaded on the International Toxicity Estimates for Risk (*ITER*) database once the authors address the issues raised.

Individual reviewers provided final thoughts. One reviewer noted that the document was well done and it was a good piece of work, in some cases going into new ground. Another reviewer had similar impressions but was a little uncomfortable with the statements of no risk, given the increased DNA adduct levels. This reviewer would like to see more of the DNA adduct work in the main analysis and animal appendix, specifically the Godschalk study. A third reviewer thought the document was magnificent, it showed high competence in the art and science of risk assessment, both in the interpretation and communication of the information. Another reviewer

agreed with this; although noting that the Pittelkow study had weaknesses, this reviewer acknowledged these have been addressed and captured in the uncertainty analysis. The next reviewer reminded the panel that the epidemiology database is large and demonstrates no concern for coal tar based shampoos or ointments. This reviewer felt that this is a state-of-the-art assessment. Another reviewer agreed and thought the authors had done their best to turn over every stone; this reviewer was satisfied the authors had done a responsible job. The next reviewer thought it was a good piece of work and was privileged to be a peer reviewer. The preponderance of the epidemiology data supports the risk levels in the report. The last reviewer agreed that it was a very good piece of work.

The Chair indicated that since the panel has agreed that a summary of this assessment can be included in the *ITER* database, the *TERA* staff will work with the authors to prepare this summary and the panel will have an opportunity to review and comment. Several panel members indicated they had specific editorial comments they would like to share with the authors. The Chair asked the panel members to send editorial comments to *TERA* and these would be forwarded to the authors.

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Attachment A

MEMORANDUM

To: Mike Dourson, Jacqueline Patterson
From: Annette Shipp, Bruce Allen, Harvey Clewell
Date: July 14, 2000
Re: Disposition of Comments on the Second Draft Report

The attached document is intended to describe revisions to the document and analyses in response to comments received from the peer review panel on our document entitled, "Estimation of Lifetime Skin Cancer Risk From the Use of Coal Tar-Containing Shampoos - TERA Review Draft." The first section of the memo is organized by general topic or issue, while the second section refers, by line number, to the final draft of the meeting minutes. Other than grammatical changes, all substantial changes are in bold.

Disposition of Comments

Part I. Changes to the Original Analyses

1.0 Estimation of the NSRL Using the Pittelkow et al. (1981) Study

1.1 Revisions to the Main Monte Carlo Analyses.

The following changes have been implemented as part of the main Monte Carlo analysis of the Pittelkow cohort and will be included in Chapter 3.0, as discussed with the peer review panel:

- ***Distributions for observed and expected incidence rates***. In response to comments on lines **276-283, 586-592, 594-599, 601-609**, distributions were created for both the observed incidence and the expected incidence as follows.

    - The distribution for the ***expected incidence*** had a range from 15.5 cases to 49.6 cases, which varied with the location. The average value for the underlying distribution of the expected incidence in the four cities of was 26.6. The incidence rate for each city was assumed to contribute equally to this average. **A normal distribution was assumed for these expected values with a mean of 26.6 and a standard deviation of 3.5. This distribution was truncated at 15.5 and 49.2. Such a distribution gives greatest weight to the average value in four locations but includes values over the entire range. Choice of other distributions, such as a uniform distribution or a triangular distribution with the most likely value of 26.6 yielded a 95th percentile on the potency estimate of less than zero, indicating no risk at all.** This distribution actually gives less weight to the Dallas-Fort Worth expected rates (representative of the sunbelt states) than is justified by the data. Using the information in Table 3, it can be estimated that roughly 35% of the years of follow-up occurred in sunbelt states.[1]

    - The distribution for the ***observed incidence*** was determined to be a custom distribution determined as follows. The observed incidence in the Pittelkow cohort was 19 and consequently, the best estimate of the true incidence is 19/260.

[1]From the information as to years living in the sunbelt after first treatment at the clinic, it was reported that 8 persons with skin cancer (50% of the 16 responding to the follow-up questionnaire or interview) had a median residence time in the sunbelt of 14 years, while 58 persons without skin cancer (46% of 125 responding to the follow-up questionnaire or interview) lived in the sunbelt for a median of 15 years. Assuming that those not giving a duration in the sunbelt (a total of 75 people) had no residence in the sunbelt, these results suggest that the average number of years of residence in the sunbelt was almost 7 years per person (letting medians estimate averages for this rough calculation). Since the mean duration of follow-up was 20.1 years per person for all the cohort, residence time in the sunbelt represented about 35% (7/20.1) of the total follow-up time.

However, a distribution was constructed that assessed the likelihood that the true expected number in a cohort of 260 persons so exposed could be a value other than 19. Assuming a Poisson distribution, the probability that the underlying mean of the Poisson distribution would be some number other than 19 for a population of 260 persons can be determined. It was those probabilities that defined the distribution for possible values of the underlying mean and from which alternative values were sampled in each iteration of the simulation. Operationally, the distribution of numbers sampled ranged from 15.5 (we were not interested in a complete characterization of values below that level) to 39.9 (the probability of a value greater than that being the true mean is vanishingly small).

- ***Days of Hospital Treatment.*** The distributions for the duration of hospital treatment (lines **554-560**) were redefined; the peaks of the triangular distributions were adjusted so that the medians of the distributions matched those reported in Pittelkow et al.

- ***Days of At Home Treatment <50 days per year.*** The lower bound on the distribution for days of at home treatment was set at 10 with a maximum of 50 days treatment per year (lines **702-711**).

- ***Lifetable Analyses.*** In response to the comment on lines **808-812**, the lifetable analysis began at ages less than one year and included four new groups: <1, 1 to 4, 5 to 9, and 10 to 14 years, **and included up to 70 years of age.**

- ***Persons Lost to Follow-up.*** Twenty of the original 280 patients were unavailable for follow-up. The cohort size used was 260 and all analyses were based on these 260 persons, including estimation of the distribution of observed incidence rates (line **822**).

- ***NSRL expressed as absorbed dose.*** In response to comments on lines **735-790, 838-842, 1074-1075, and 1117-1118**, exposure to constituents in pharmaceutical grade coal tar will be expressed as the absorbed dose rather than the applied dose. The following data will be used to estimate the absorbed dose.

    - ***1-hydroxypyrene in urine of psoriasis patients.*** Analogous to the urinary excretion data for shampoo users reported by von Schooten et al. (1993), urinary excretion data of 1-hydroxypyrene (1-OHP) for psoriasis patients treated using the Goeckerman therapy (pharmaceutical grade coal tar and UV) in clinical settings were available (Santella et al. 1993). In the Santella et al. (1993) study, **53** psoriasis patients were recruited from inpatient service at Columbia-Presbyterian Medical Center. Patients were treated according to the Goeckerman therapy: pharmaceutical grade coal tar was applied to the entire body surface at least once a day followed by UVB treatment. Individual exposures were not reported, since the ointments were self applied; however, the authors reported that exposure ranged from 20 to 100 gm of ointments/day per patient for an ointment that contained 700 mg pyrene/kg ointment. Based on these estimates, the daily applied amount of pyrene was 14 to 79 mg pyrene/day (69 to 346 µmoles

pyrene/day). 1-OHP levels in twenty-four-hour urine samples collected from each patient following at least three days of therapy were compared to 1-OHP levels in 45 age-, sex-, smoking status-matched volunteers with no exposure to coal tars. In psoriasis patients, the mean 1-OHP levels were 546±928 µmoles/mole creatinine with a range of 10 to 5160 µmoles/mole creatinine, while levels in volunteers ranged from 0.02 to 0.98 µmoles/mole creatinine with a mean value of 0.14±0.17. Two distributions were sampled - **as indicated by the study authors, one a log-normal distribution with the study reported mean and standard deviation for 53 patients. A second log-normal distribution for pyrene applied was obtained by scaling up the log-normal distribution for the 1-OHP excretion data.** The resulting distribution would represent the amount of applied pyrene that was systemically available and excreted in the urine. According to Viau et al. (1995), one way absorption of constituents in coal tar can be defined is as the percentage of the applied pyrene that is eventually eliminated in the urine as 1-OHP.

- ***Estimates of Amount Absorbed.*** The distribution described above is expressed in units of the 1-OHP excreted in the urine, which can be described as a biomarker of exposure. To express the NSRL in units of amount of coal tar constituents absorbed, a distribution of the fraction of absorbed pyrene that is metabolized to 1-OHP and excreted in the urine must be calculated. At the request of the reviewers (lines **989-1008**), the data for the term F_e, absorbed fraction that is excreted, was revisited. We maintain that an upper bound of 81% (note - the larger the fraction excreted, the lower the amount of pyrene absorbed) is supported by the data on human metabolism and excretion of pyrene and additional justification **was** provided in the text. Dr. von Rooij was contacted and confirmed that more than 90% of the 1-OHP produced was excreted in the urine following application of coal tar ointment. **Human fecal data were received from Dr. von Rooij and reviewed to confirmation that 1-OHP levels were not detected in the feces of his volunteers as reported in von Rooij et al. (1993)**. However, the lower end of that distribution was revised based on the oral administration data reported by Viau et al. (1995). If it is assumed that virtually 100% of the pyrene administered orally (a bolus dose of 500 µg pyrene in 3 ml of olive oil) was absorbed, then the amount of absorbed pyrene that was recovered in the urine as 1-OHP was approximately 3% to 4.5%. Therefore, 3% will be used as the lower bound for **a uniform distribution with 81% as the upper bound**. It is important to note that estimates of absorbed amount are being estimated for both psoriasis patients and for shampoo users in an identical manner. It seems reasonable to assume that once pyrene is absorbed, the metabolic fate of the pyrene - metabolism to 1-OHP and excretion of 1-OHP in the urine - is the same for patients and shampoo users. Consequently, the same distribution for F_e will be used for both groups.

1.2 Sensitivity and Uncertainty Analyses

As indicated by the peer review panel on lines **322-330 and 832-836**, a sensitivity analysis with cross-categorization as to priority was conducted. Alternative assumptions for the key parameters as well as those identified by the panel as potential uncertainties in the Pittelkow data (lines **285-292; 326-330; 792-799; 824-842**) were investigated. All of these discussions will be included in the Risk Characterization section of the document.

- ***Sensitivity Analyses.*** The sensitivity analyses were conducted as follows. Each of the parameters in the equation to estimate intake and potency was qualitatively assigned an ordinal value based on degree of uncertainty, e.g., a parameter identified as a 3 was more uncertain than one assigned a 1 but not three times more uncertain. Then the estimates of both dose and the 95% upper bound on potency were estimated by increasing the value of one parameter by 10% and holding all other parameters fixed. The parameters were then ordered according to impact on both dose and potency and combined with the qualitative ranking to identify those parameters that had the greatest impact on dose and potency as well as the greater uncertainty. These parameters were then considered further in additional analyses in which an alternative assumption(s) regarding the parameter was considered. This will be discussed in the Risk Characterization section.

- ***Analyses Using Alternative Assumptions***. The following assumptions were evaluated by considering different underlying distributions.

  - ***Expected and Observed Incidence Rates***. As discussed by panel members (lines **581-584, 609-609, 792-799, 801-807, 824-830**), the potential for underreporting of observed cases in the Pittelkow cohort should be considered. As noted in that study, incidence rates were derived from medical records, interviews and questionaires, and interviews with family members of deceased members of the original cohort. It is unknown how many of the reported cancers were contributed by members alive at the time of follow-up. This uncertainty is being handled both qualitatively and quantitatively and will be discussed in the Risk Characterization section. On the **qualitative side** we have: 1) contacted the original study author, Dr. Pittelkow, and await his reply, hopefully; 2) conducted a literature search to ascertain reporting bias from family members for diseases in deceased relatives; and 3) have re-reviewed the epidemiology data to get a sense of this issue in other studies.

    Cases in the literature. The literature search produced several articles, which are being retrieved. One study by Aitken et al. (1996) evaluated the reporting bias of relatives of patients with melanoma and found a 40% false-positive rate, i.e., over-reporting. However, other skin cancers may have been confused with melanoma accounting for some of the false positives. Also published by Aitken et al. (1995) the validity of family reporting was assessed for colorectal cancer. Reports of colorectal cancers in family members were confirmed in only 77% of the cases, i.e., a 22% false-positive report, while 98% of the negative responses by a family member were correct. Breuer et al. (1993) assessed the validity of family reporting for breast cancer in relatives. They found

that family members that reported unilateral breast cancer in a first-degree relative were correct 94% of the time, or those who reported either unilateral or bilateral breast cancer in a living relative were correct 94% of the time, but relatives who reported that a deceased relative had bilateral breast cancer were only correct 62% of the time, i.e., 38% false-positives.

Over or Under-reporting in other Clinical Epidemiology Studies. Only Stern et al. (1985) addressed this issue. His comparative study found that patients with psoriasis were found to be at greater risk of basal cell carcinoma but that increase could not be attributed to any one particular factor (ionizing radiation, sunlamp, coal tar, fair skin) and noted that the finding may have been a result of "surveillance bias" because of the closer dermatologic scrutiny received by these patients.

On the **quantitative side**, **two** alternative assumptions as to the observed incidence were used as the starting point to determine the distribution of the true incidence rate. In spite of the potential for "surveillance bias" and the lack of strong evidence of under-reporting by family members (in fact, the initial impression is that over-reporting is more common), a 10% increase in the observed incidence was considered. The starting value of the observed distribution was 21. **Because other factors suggest over-reporting, another analysis was conducted with a starting value of 17 for the observed distribution.** These results **are** discussed in the Risk Characterization section.

- ***Assigning the Unknowns.*** As indicated in lines **285-292, 541-544, and 611-624**, not all of the 260 persons in the cohort responded to questions regarding coal tar use at home - both whether or not used and for how many days per year. **The sensitivity analyses indicated that a possible reassessment** that the probability of falling into each one of the treatment categories was 0.3 **would have little effect on the potency estimate. No further action was taken**. After further thought, a bounding estimate in which all were assigned to one of three categories was considered unrealistic and unlikely to provide useful information.

- ***Fraction of the Body Treated at Home.*** In response to comments on lines **676-692**, another assumption regarding the surface area treated at home was evaluated. A triangular distribution with a minimum and maximum of 5 and 30, respectively, and a peak of 30 was considered. This is based on the suggestion from a panel member that the mean surface area treated at home is 30%, but modified to account for other suggestions that the original range from 5 to 25% was not unreasonable.

- ***Days of the Year Greater than 50.*** Alternative assumptions in which a triangular distribution with a peak of 150 days/year were evaluated to compare to the assumption in the main analysis of a uniform distribution that has a mean of 208 days/year (4 days per week).

C ***Alternative Distribution for Expected Incidence Rates.*** As an alternative to the use of the **normal** distribution discussed above, we assumed a triangular distribution for the individual contributions to the expected numbers of skin cancers. The most likely value for the triangular distribution was the mean calculated from the rates reported in Pittelkow et al. (1981).

C ***Alternative Distribution for Percent Coal Tar Used at Home.*** As an alternative to the uniform distribution ranging between 2% and 5%, the alternative selected was a triangular distribution with a minimum of 2%, a maximum of 10% and a most likely value of 6% (lines **663-674**). This distribution accounts for some of the suggestions that the percent coal tar in ointments has historically been above 5%, but gives those possibilities less weight (because they did not appear to be tolerated well).

C ***Alternative Distribution for the Amount Absorbed.*** The calculation of the fraction absorbed depends on three factors known only with uncertainty: the amount of 1-hydroxypyrene excreted in the urine, the amount of pyrene applied in the ointment, and the fraction of absorbed pyrene that is metabolized and excreted as 1-hydroxypyrene. An alternative distribution was selected for each of the distributions representing those uncertainties. For the excretion of 1-hydroxypyrene, a **normal** distribution **having the same mean and standard deviation distribution as was used in the main analyses was chosen as an alternative.** For the amount of pyrene applied in the ointment, a **normal** distribution replaced the **log normal** distribution of the main analysis; the **log normal** distribution had the same **mean and variances as the main analyses**. Similarly, for the fraction of absorbed pyrene metabolized to and excreted as 1-hydroxypyrene, the uniform distribution of the main analysis was replaced by a triangular distribution having the same endpoints and a most-likely value at the midpoint.

2.0 Issues Related to Estimates of Exposure for Shampoo Users

The following changes in the Exposure Assessment for shampoo users will be applied and reported in Chapter 4.0

- ***Usage Per Year***. In response to comments on lines **1010-1023 and 1025-1039**, estimates of ounces of shampoo used per year will be based on total coal tar containing shampoos as reported by the Nielsen Home Market survey. The Toppmeyer Survey (1994), which reports only the use of Denorex shampoo **was not** used (given the larger sample size of total coal tar containing shampoo users from Nielsen, would have little impact if included). Marketing data from Nielsen for Denorex products confirmed that these purchasing patterns were consistent with sales. Further, it has been confirmed that Neutrogena markets 1 oz and 3 oz trial-size bottles. Usage/sales data is being sought from Neutrogena.

- ***Years of Exposure***. In response to comments on lines **1059-1072**, we re-evaluated the number of years of usage of any of these products. In the Toppmeyer survey, responders were asked the number of years they had suffered with the condition specified. This was thought to be a more reliable measure of product usage than recall as to the number of years a product had been used. However, this response - number of years with condition - represented a "snap shot" up to that time. Consequently an analysis **was** done in which the age of the individual at the time of the survey and the number of years with the condition **were** used in a regression analysis to project usage for a 70-year lifetime. **The results of this analysis indicated that the mean usage was 18 with a 95% upper bound on that distribution of 42 years**. **The range of years of usage (exposure) was increased to range from 1 to 70 years.**

- ***Estimates of Absorbed Dose.*** Estimates of absorbed dose for shampoo users **was** estimated in the same manner as used for the psoriasis patients. A distribution of the total urinary excretion of 1-OHP (over the 48-hour follow-up) **was** constructed from Van Schooten et al. (1994). Closer inspection of the data indicated that these data are log-normally distributed, based on the amount excreted on day one following application (range of 0.4 to 8.3 µmoles 1-OHP/mole creatinine and a calculated mean value of 1.3 µmoles 1-OHP/mole creatinine). Based on this data, the total excretion of 1-OHP would be a mean of 29 nmoles, with a standard error on the mean of 3.03, based on the largest standard error associated with a given time point on the excretion curve. The same distribution of fraction excreted, F_e, as was used for the psoriasis patients **was** assumed for shampooers. Knowing the amount of pyrene applied, then, the distribution of the applied amount that is absorbed **was** estimated.

- ***Estimates of Typical Intake.*** The summary output values reported from the Monte Carlo analysis were median exposure estimates for each of the selected percent coal tar shampoos (0.5% to 2.5%). The median is the appropriate measure of a "typical" user. Compared to the median user, any other user is equally likely to have had a greater exposure or to have had a lesser exposure. Because the output distribution is intended to represent variability over individual users (as a consequence of the fact that the input distributions represent variability over individuals) it is not appropriate to characterize the typical user by the mean of the output distributions. That measure of central tendency would only be appropriate if the distribution represented quantities that are somehow "added together" to yield a composite. Each point of the output distribution represents the possible exposure of one individual and no adding together or averaging of those points is required.

3.0 Issues Related to Children

Since psoriasis may occur in children, there were questions raised that children may be users of coal tar-containing shampoos and that their lifetime risk may not be adequately characterized if only adult exposure is considered (lines **261-269; 570-579, and 1089-1115**).

This uncertainty was addressed in several ways:

- In response to the comment on lines **808-812**, the lifetable analysis began at ages less than one year and included four new groups: <1, 1 to 4, 5 to 9, and 10 to 14 years. As stated above, this was included in the main analysis discussed in Chapter 3 - Dose-Response Assessment.

- The uncertainty that exposure as a child would engender a higher extra lifetime skin cancer risk considered two components: a potential increase in the sensitivity of child's skin to constituents in coal tar and a potential increase in the total lifetime exposure.

- With regard to the potential for increased sensitivity of infant or child skin, the following evidence was considered (lines **1089-1105**) and will be discussed in the uncertainty section:

  - Basal AHH activity levels are comparable in neonatal foreskin and adult epidermal skin sections (0.1 and 0.06 pmoles 3-OH BaP/min/mg protein, respectively) and responded similarly (about a 3-fold increase in AHH activity) following induction with benz(a)anthracene (Alvares et al. 1972; Bickers et al. 1984; Levin et al. 1972).

  - Neither human fetal skin nor adult skin xenografts developed tumors following application of DMBA with TPA promotion (Graem 1986). Production of squamous cell carcinomas was noted in **2/43** human neonatal xenografts following DMBA and UV-B treatment but not in 13 adult xenografts similarly treated (Soballe et al. 1996) suggestive but not clear evidence of an enhanced response in neonatal skin (a Fisher's Exact test fails to reject the null hypothesis of no difference, $p = 0.61$).

  - DNA repair rates are comparable in human fetal skin and adult skin with adult skin removing 50% of UV-induced pyrimidine dimers over a 16-hour period and fetal skin removing 65% of pyrimidine dimers over a 24-hour period (Gibson-D'Ambrosio et al 1983; Taichman and Setlow 1979).

  The review of the available literature provided no clear evidence of an increased sensitivity of infant or child skin compared to adult skin. These data were discussed qualitatively in the Risk Characterization section.

C With regard for the potential for increased lifetime exposure, the following was considered and was discussed in the uncertainty section.

  C Estimate of exposure would be higher in children if the absorption into the skin of children was greater than that of adult skin. Singer et al. (1971) determined that in mammalian species the stratum corneum, which is considered to be the barrier layer to absorption, was fully developed at birth and at birth the ultrastructure of the stratum corneum, was indistinguishable from that of the adult. Their data in

rats and guinea pigs indicated that the development of the stratum corneum starts in the last quarter of gestation and is completed just before term, which would explain why transient differences in absorption were noted in premature infants compared to adults. Wester et al. (1977) found dermal absorption of testosterone in newborn and adult Rhesus monkeys was not significantly different. Further, Cunico et al. (1977 as cited in Rasmussen 1979) reported no differences in two parameters indicative of skin penetration rates when 22 term infants were compared with 30 adults.

- Consequently, no separate analysis, as suggested on lines **1100-1105**, to incorporate differences in absorption across ages will be conducted. Rather, the estimates of LADD from shampooing will assume that the amount of shampoo used by children and adults is the same (i.e., differences in surface area that may translate into less shampoo use by children was not considered) and the years of usage was expanded to range from less than 1 to 70 years.

4.0 Issues Related to the Use of the Mouse Data

1. Development of an Appendix

The panel agreed that the mouse data are not an appropriate basis for a model to estimate human cancer risk from exposure to coal tar shampoos; however, additional discussion on this issue would have been beneficial (lines **369-385**). The panel also reached unanimous consensus that the animal analysis should be included in an Appendix for comparison purposes only and that the limitations should be made more explicit in the discussion. In response to these concerns, an appendix is being developed that contains the quantitative analysis using the mouse data. The text is being revised to indicate that this analysis was conducted for comparative purposes, as well as indicated that any quantitative estimate using the mouse data would be a "ball park" estimate.

2. Estimation of the Uncertainty in the Mouse NSRL

In addition to de-emphasizing the mouse analysis by moving it to an appendix, the panel also requested that an assessment should be conducted to include some uncertainty bounds around the mouse estimate to give readers an understanding of how imprecise the mouse estimate could be (lines **369-385, 437-445, 870-878**). This request is being addressed by conducting a Monte Carlo analysis to develop a distribution of NSRLs based on the mouse data. Distributions have been developed for each parameter involved in the estimation of a Human Equivalent Dose (HED) for each of the mouse bioassay doses in the following equation with the exception of the applied amount and the pharmacodynamic adjustment factor (PAF). With the currently available data, one cannot bound the uncertainty in the pharmacodynamics between species, and a distribution would provide a perception of accuracy greater than is appropriate given the data. The value selected for PAF (the fraction of total body surface to which coal tar is

applied) represents a worst-case assumption that human skin has the same susceptibility as mouse skin to the carcinogenicity of coal tar constituents, an assumption which is contradicted by the mechanistic and xenografts data discussed in the main report.

$$HED(\ g/day) = AA * \left[\frac{\frac{FA_A}{FA_H} \times \frac{AHH_A}{AHH_H} \times \frac{CL_A}{CL_H}}{\frac{SV_A}{SV_H}} \right] * \frac{PAF_A}{PAF_H}$$

where:

AA	=	Average daily applied amount in the animal dose group of the bioassay (µg/day)
FA	=	Fraction of applied dose that is absorbed (unitless)
AHH	=	AHH activity (pmol/min/mg protein)
CL	=	Clearance from the skin compartment (mg/cm^3)
SV	=	Volume of the skin at application site (cm^3)
PAF	=	Fraction of total body surface area to which coal tar is applied (unitless)

In the original dose-response analysis, a Multistage Weibull time-to-tumor model was used to account for the much shorter duration of exposure in the 9 mg/day dose group and for the less than lifetime exposure (78 weeks) for the remaining dose groups. However, because this analysis was intended to give an idea of the potential uncertainty in the estimate and because the Multistage Weibull model could not be readily used in this type of analysis, the high dose group was removed from the analysis and the Multistage model used with a crude time-to-tumor adjustment [(duration of study/average lifespan)^3]. To insure that this analysis did not result in an NSRL estimate vastly different from the original value (11,300 µg coal tar/day), the HEDs and tumor incidence used in the original analysis for all of the dose groups (excluding the 9 mg/day group) were used in a dose-response analysis using the Multistage model with the crude time-to-tumor adjustment. The resulting NSRL (10,500 µg coal tar/day) was slightly more conservative, but consistent with the NSRL estimated using the Multistage Weibull model.

For the Monte Carlo analysis, a brief description is provided below of the distributions used for each of the parameters in the equation shown above. A more detailed description will be provided in the new appendix of the document containing the analysis based on the mouse data.

-
- FA_A — Mean: 0.63
  SEM: 0.082
  Distribution: truncated normal
  Basis: Storm et al. 1990

- AHH_A — Mean: 11.5
  Min: 8.33

Max: 16.43
Distribution: triangular
Basis: Thompson and Slaga (1976); Kinoshita and Gelboin (1972); Das et al. 1986a

- AHH_H Mean: 0.7
  Min: 0.165
  Max: 2.29
  Distribution: triangular
  Basis: Levin et al. (1972); Alvares et al. (1972) Bickers et al. (1984); Das et al. (1986a); Bickers and Kappas (1978)

- CL Mean: 0.15 (Assumes relationship of clearance between mice and humans scales by $BW^{3/4}$)
  Min: 0.034 ($BW^{9/16}$ - assumes clearance of parent scales by $BW^{3/4}$ and clearance of metabolite scales by $BW^{3/4}$)
  Max: 1.0 (BW^{1})
  Distribution: triangular

- SV_A Mean: 0.0108
  Min: 0.0095
  Max: 0.0121
  Distribution: triangular
  Basis: Fraunhoffer (1997) reported that 10% of the total body surface area received administration; no information on variation, assumed this could vary by ± 2%; Klein-Szanto et al. (1991) reported the depth of mouse skin to be 0.003 cm; assumed this could vary by ±10%.

- SV_H Mean: 41
  Min: 30.75
  Max: 51.25
  Distribution: triangular
  Basis: USEPA (1997); Klein-Szanto et al. (1991); ICRP (1975)

For comparison to the new NSRL estimated for Pittelkow expressed as absorbed dose, an NSRL based on the mouse data that was expressed as absorbed dose was needed. In order to provide a ball park for comparison, the adjustment for fraction of applied dose that is absorbed in the human (FA_H) was removed from consideration in the above equation, resulting in HEDs expressed as "absorbed dose."

For each iteration in the Monte Carlo analysis, each of the above distributions was sampled to develop one set of HEDs associated with the animal bioassay doses reported in Fraunhoffer (1997) (0.1, 0.3, 1, and 3 mg/day). The HEDs and incidence data for skin tumors from Fraunhoffer (1997) was then incorporated into TOX_RISK for Windows and the Multistage model fit to the data to estimate the lower bound on dose associated with a 1 in a 100,000 risk.

This process was repeated for 100,000 iterations, resulting in the development of a distribution of NSRLs expressed as absorbed dose.

The resulting distribution of NSRLs based on the mouse data, and expressed as absorbed dose, had a median or 50^{th} percentile of 58.5, with a 95^{th} percentile of 300 and a 5^{th} percentile of approximately 9. Therefore, it appears that the "ball park" NSRL based on the mouse data could vary by at least a factor of approximately ±6. However, this range of estimates is based on the worst-case assumption (PAF=1) that the mouse and human are equally susceptible to the carcinogenicity of coal tar constituents. The mechanistic and xenografts data discussed in the main report clearly indicate that the human is much less susceptible, if at all, to these effects. Therefore, this range represents the lower bound on an uncertainty distribution for the NSRL that has infinity as the upper bound.

Part II: Response to Specific Draft Meeting Minutes Comments

This is the planned action/response to comments/questions in the final meeting minutes that were not already addressed in Part I. For any lines/sections not included, no response was necessary.

Line No.	Comment
243-259	These comments referred to the discussions of the occupational data. The following were done: 1) Maizlish et al. (1988) and Hanson et al. (1989) were deleted for the stated reason; 2) Studies for cutting oil workers (Hendrick et al. 1959; Jarvholm and Lavenius 1987; Jarvholm and Easton 1990; and Jarvholm et al. 1985) were reviewed; 3) a study for foundry workers (coke oven) (Sherson et al. 1991) was included; 4) studies of aluminun plant workers (Spinelli 1991; van Rooij et al. 1992; Ronneberg and Andersen 1995) were reviewed for exposure data; and 5) Letzel et al. (1998) was reviewed. These studies **were** included in the text (briefly in Chapter 2.0 and in more detail in Appendix A. **The study with exposure data for aluminum workers was in a different factory and different country than the study for which cancer incidence data were reported. In that study, no increase in skin cancer incidence rates were noted. We did not attempt to use these data quantitatively.** None of the studies provided a clear association between exposure to coal tar derived products and skin cancer.
271-274	This question referred to systemic tumors as a result of dermal application. The literature was re-reviewed. In occupational studies, there were no reports of systemic tumors (i.e., lung, bladder) in cohorts that did not also have concomitant exposure to these coal tar-derived materials by the inhalation route. Therefore, the contribution from the dermal pathway alone could not be assessed. In the clinical epidemiological studies, Pittelkow et al. (1981) reported that the range of malignant systemic tumors was in "concordance with the commonly found tumors reported in the survey." Jemec and Osterline. (1994) reported that the use of coal tar to treat atopic dermatosis did not increase the risk of systemic tumors. No further action was taken
294-313	In response to questions about the applicability of psoriatic skin, additional data that compares psoriatic skin and "normal" skin will be added to the text. Information such as the metabolic capability of both skin types to form the ultimate PAH metabolites (same for both) or the induction of ODC following application of pharmaceutical grade coal tar (none for both). **Additional discussion of these differences was included in Section 2.2.2.1. Discussion structured according to conditions for comparison noted by Dr. Emmett (lines 225-234)**

315-318	A **brief description was** added to the text to describe the different mixtures and the text will be clarified as to which mixture was evaluated (primarily for animal and occupational data). Information was provided by the sponsor that the FDA monograph for USP Pharmaceutical Grade coal tar has been in place since 1955. **This is mentioned in the Risk Characterization section.**
342-347	**The xenograph studies were revisited. However, none of the data was presented in a way in which interhuman variability could be assessed.**
350-354	**This comment referred to a paper by Nesnow and Lewtas (1991) and indicated that was the basis for the statement regarding correspondence between mouse skin painting studies and human studies. This paper is being reviewed.**
363-367	**The document now clearly states that mouse data should not be used.**
369-378	The panel commented that none of the animal studies were suitable for a risk assessment of coal tar, because the animal studies used mixtures which are dissimilar from coal tar. These mixtures contain components which may cause skin irritation or act as promotors. The panel requested that these differences be acknowledged and discussed in the risk assessment. The text **was** expanded to further clarify this point and to indicate that the relevant coal tar mixture for shampoo has not been tested.
396-400	One reviewer suggested a discussion about the mode of action for skin cancer to address the question of the proper dose metric for predicting carcinogenicity of PAH mixtures. This reviewer also questioned whether AHH enzyme activity is the appropriate measure of carcinogenicity. The use of AHH enzyme activity in the development of an NSRL based on the mouse data is one of the components of quantifying the potential pharmacokinetic differences between the mouse and the human. The capacity of the AHH pathway in both species is thought to be the rate-limiting step for the development of the carcinogenicity moiety. The use of the capacity of this enzyme is used as a comparison of the capacity between the animal and human as a ball park estimate of the potential of each species for development of the carcinogenic moiety. This is combined with other factors, such as the rate of clearance from the skin, to quantitatively describe the potential pharmacokinetic differences between mouse and humans as it relates to the development of skin tumors following exposure to PAHs. This **in Appendix E, the appendix with the animal model,** text **was** expanded to further clarify this issue.
406-409	**One reviewer suggested that a predictive model for carcinogenicity based on PAH content could be explored. This was not feasible for complex coal tar mixtures that differ widely since the activity is influenced by more than the PAH content.**

457-460	While we agree with this comment with regard to the data provided in Section 2.3, to provide clarification to address this comment, we **revisited** the animal and occupational data and **identified a few mixtures evaluated in common.** New information that will be included in the section on tumor promotion demonstrated that application of pharmaceutical grade coal tar to the skin of psoriasis patients or to volunteers did not produce an increase in ODC levels, in fact a 21% decrease was noted. Coal tar applied to mouse skin did result in a significant increase in ODC levels.
462-468 **491-494**	One reviewer requested that the variability seen in the response of various mouse strains to the carcinogenicity of PAH mixtures should be better characterized. There are no bioassay results to conduct such an assessment; however, there are data from tumor promotion and xenografts studies that can address this question. These studies are being reviewed again and the text is being expanded to address this question. **Data on AHH induction and tumor promotion differences among mouse strains was reviewed and included in the document. The data for human xenografts was re-visited to try to identify variability in human responses; however, no data were reported that allowed for that.**
470-477	As requested, a stronger statement regarding the differences in promotional mechanism between mouse and human **was** added to the text.
570-579	The ages of patients at the time of the initial Goeckerman therapy were not given in the text of the Pittelkow et al. paper; therefore, it is not known if any of this cohort began treatment as a child or young adult. It was stated that 67% and 68% of those without skin cancer and those with skin cancer, respectively, had coal tar treatments prior to enrollment at the Mayo Clinic for the first time in 1950. It was also stated that the median age of patients who developed skin cancer was 59 years with a range of 39 to 92 years. The median number of years of treatment after the initial Goeckerman therapy and the development of skin cancer was 20 years with a range of 4 to 27 years. Consequently, for the individual who was 39 when the skin cancer developed, the initial treatment at the Mayo Clinic could have begun as young as 12 years of age (if he had the longest time to tumor) or as old as 35 (if he had the shortest time to tumor). Consideration of exposure to children was considered as indicated in Part I. It should be noted that ignoring exposure prior to the initial Goeckerman therapy is likely to be a health-conservative assumption (resulting in a lower NSRL than trying to include it).

631-638	It was noted in comments on lines 621 to 628, that the sex of the participants in the Pittelkow study was not provided. The only gender-specific parameter used in the assessment of coal tar exposure to the cohort was body surface area. To address this comment: 1) The study author, Dr. Pittelkow, has been contacted to ascertain the number of men and women in the study; however, we have not yet **had an opportunity to speak with him**. 2) Other studies were rechecked and in those other clinical studies in which the gender of the cohort was reported, approximately an equal number of men and women were represented. For example, Bhate et al. (1993) reported 995 men and 1252 women, Jones et al. (1985) reported a cohort of 305 men and 414 women, while Stern et al. (1995) reported 897 men and 483 women. In the study by Alderson and Clark (1983) in which the incidence rate was evaluated separately for men and women, the relative risk ratio was slightly lower in women (1.06) compared to men (1.26); however, neither group was significantly different from the control population. **Muller and Perry (1984) report on page 267 the results of their 1968 Mayo clinic patients – 120 total (60 men and 63 women).** In the Bhate et al. (1993) study, the incidence of skin cancer in women was greater than that reported for men, although the authors noted that women, in general, received more treatments of all types than men. 3) **The National Psoriasis Foundation web site indicated a slight increased prevalence among women**. 4) The only gender-specific parameter used in the analysis was body surface area, which was described with a mean of 1.84 $\pm$.23. The surface areas for women and men have a mean of 1.72 $\pm$.18 and 1.95 $\pm$.18, respectively. If it was assumed that all of the participants were women or all were men, then the estimated NSRL would be slightly lower in the former case and slightly higher in the latter case, but it is unlikely that this difference would be significant. No further action **was taken**.
640-646	Use of shampoo in addition to the coal tar therapy for psoriasis patients was not included. This **was** addressed the Risk Characterization section as one of the factors that may indicate that estimates of exposure to the psoriasis cohort could be an underestimate.
715-720	The average years of follow-up for persons who died during the follow-up years was estimated to be 13 years based on the total years of follow-up. For the persons who did not have cancer, the median value of the distribution used is 14, consequently, those individuals who died during follow-up years would appear to have had years of follow-up (treatment) that correspond nicely with the assumed distribution. No further action is planned.
722-727	**Additional discussion on the topic of power was added to Sections 3 and 5.**
729-733	**Added a discussion of assumption of linearity to uncertainty discussion in Section 5.**
814-820	The ratio of SCC and BCC and the implications of a change in that ratio will be discussed qualitatively in the Risk Characterization section **in the final document**.
1013	These values are Nielsen's extrapolation to the entire US population and should read 44 million and 8.1 million. The actual number of households in the survey for coal tar users was **3200 households.**

1041-1049	One of the observers stated that an EU document assumed that 102 oz per year was used by shampooers. We have located that document. First, the value of 102 oz per year is for any shampoo product and was not specific for coal tar shampoos. Secondly, the EU, when they use these data to estimate exposure, assume that only 10% of the amount applied comes in contact with the scalp; therefore, only 10 oz per year is available for absorption. We are assuming based on a revised analysis of the Neilsen data that the distribution for ounces per year has a mean of 7.4 and all of that is available for absorption. More than 20% of the sampled values for ounces per year would be greater than 10 (ranging up to 136) using the selected distribution, so our analysis would include cases even more conservative than those posed by the EU.
1055	**We are still awaiting sales data from one sponsor.**
1056-1057	**This assumption is mentioned in Risk Characterization – Section 5.**
1226-1236	**Last sentence removed from document.**