ITER Peer Review on Acrylonitrile, Cadmium, Chromium Meeting Summary

December 16 and 17, 1996

Reviewers

Dr. Stuart Baxter, University of Cincinnati
Dr. Robert Benson, U.S. EPA
Dr. Matthew Bogdanffy, Haskell Laboratory, DuPont
Dr. John Christopher, California EPA
Dr. Gary Diamond, Syracuse Research Corporation
Dr. Michael Dourson, Toxicology Excellence for Risk Assessment
Dr. Linda Erdreich, Bailey Research Associates, Inc.
Dr. Marvin Friedman, Cytec Industries, Inc.
Dr. Michael Gargas, ChemRisk Division of McLaren/Hart
Dr. Kenneth Poirier, Procter and Gamble
Dr. Andrew Renwick, University of Southampton

Presenters and Chairs

Cadmium: Presenter - Dr. Gary Diamond, Syracuse Research Corporation. Chair - Dr. Michael Dourson, Toxicology Excellence for Risk Assessment

Acrylonitrile: Presenter - Dr. Susan Felter, Toxicology Excellence for Risk Assessment. Chair - Dr. Kenneth Poirier, Proctor and Gamble

Chromium: Presenter - Ms. Deborah Proctor, ChemRisk Division of McLaren/Hart. Chair - Dr. Michael Dourson, Toxicology Excellence for Risk Assessment

Review Process, Ground Rules, and Conflict of Interest

The meeting began with a review of the process, ground rules, and conflict of interest management plan. The panel agreed with the proposed plan for managing conflict of interest with the following changes: correction that Dr. Gargas should not be polled for a recommendation on the chromium file, rather than the acrylonitrile file as written; addition that Dr. Bogdanffy stated for the record that DuPont does manufacture chromium products, but he is not involved in that aspect of the company and does not think there is a conflict with his participation -- the panel agreed. The approved conflict of interest management plan is attached.

Cadmium Presentation and Discussion

Gary Diamond of Syracuse Research Corporation presented the cadmium assessment. Because of his involvement, he was not polled for a recommendation regarding the assessment. Michael Dourson of Toxicology Excellence for Risk Assessment chaired this portion of the meeting.

Presentation: Many studies in humans have examined the health effects of cadmium; these studies have involved both higher levels of exposure (primarily occupational) and environmentally exposed populations with lower levels of exposure, primarily from food. The kidney is considered the critical target organ for cadmium in exposed populations. Dose-response relationships for cadmium have been established by way of biological indices of body burden such as concentration of cadmium in the renal cortex and associated urinary cadmium levels.

A cross sectional epidemiology study conducted in Belgium (designated as the Cadmibel study) analyzed data from 1699 subjects to determine possible associations between cadmium exposure and renal effects (Buchet et al., 1990; Lauwerys et al., 1990; Lauwerys et al., 1991). The average exposure to cadmium, expressed as urinary cadmium, was 0.84 ug/24 h. Only about 11% of the subjects had urinary cadmium >2 ug/24 h. Urinary cadmium excretion was significantly and positively associated with five variables that are indices of renal tubular dysfunction: urinary excretion of beta2-microglobulin, retinol binding protein, n-acetylglucosamine (NAG), amino acids, and calcium. None of these five variables were associated with blood cadmium. A logistic regression model was developed, relating 24-hour urinary cadmium excretion to the probability that individual subjects would have values of the five variables that were above the 95th percentile for subjects without diabetes or urinary tract diseases. Estimates from the model indicated that the prevalence of values above the 95th percentile would be greater than 10% when cadmium in the urine was greater than 3.05 ug/24 h (beta2-microglobulin), 2.87 ug/24 h (retinol binding protein), 2.74 ug/24 h (NAG), 4.29 ug/24 h (amino acids), and 1.92 ug/24 h (calcium).

A biokinetic model (Kjellström and Nordberg, 1978, 1985) was used to estimate cadmium intakes associated with the 10% response for the five variables of renal tubular dysfunction. The cadmium intakes (ug/kg/day) predicted by the biokinetic model for the urinary cadmium excretion associated with the five variables are: calcium, 1.9 ug/24 h = 1.1 ug/kg/day; NAG, 2.7 ug/24 h = 1.7 ug/kg/day; retinol binding protein, 2.9 ug/24 h = 2.9 ug/kg/day; beta2-microglobulin, 3.0 ug/24 h = 3.0 ug/kg/day; amino acids, 4.3 ug/24 h = 3.1 ug/kg/day. The cadmium intake corresponding to the urinary cadmium excretion associated with calcium (1.1 ug/kg/day) was the minimal LOAEL proposed as the basis of the oral RfD. Using an uncertainty factor of 10 (3 for minimal LOAEL and 3 for database deficiencies), the proposed oral RfD is 1E-4 mg/kg/day.

Hazard Identification: Reviewers had questions regarding the manner in which individuals were included for the assessment of the parameters of renal tubular dysfunction. It was unclear if the 95th percentile cutoff determined the distinction between responders and non-responders or if this cutoff was related to some degree of abnormal kidney function in individuals. Dr. Diamond indicated that the 95th percentile

cutoff was used to distinguish responders from non-responders, thus constructing the dose-response curve. The overall response rate can then be determined from the dose-response curve. Reviewers also had questions about the criteria that were used to exclude individuals from the study. Only age was used to exclude individuals, so that the study population included sensitive subgroups such as diabetics.

In an extensive discussion of the biokinetic model used to predict cadmium intakes, reviewers expressed concern that the model did not fit the data well because it was consistently under predicting urinary cadmium. Two reasons were suggested for the poor fit: cadmium absorption is age related and the study population was not stratified by age; there were additional sources of cadmium intake in the study population (such as from air) that were not accounted for by the authors. One reviewer pointed out that these types of models generally have wide variation and that this model is actually doing a good job of predicting because it is within a factor of two. Thus, the slope of the relationship between observed and predicted urinary cadmium may not be statistically different from 1. In any case, the model is still health protective because it is over predicting dose associated with a given risk.

In response to a question on whether this approach is better scientifically than the approach used for the cadmium RfD currently on IRIS, there was general agreement that urinary cadmium is a good biomarker and that modeling urinary cadmium is a better approach than modeling the concentration of cadmium in the renal cortex. One reviewer suggested that the RfD be expressed in terms of urinary cadmium excretion. There was also general agreement that the document should provide more text which relates the urinary cadmium excretion levels back to a marker of effect. Finally, reviewers suggested including a summary of the animal data in the document to help establish the mechanisms of toxicity.

Choice of Critical Effect/Study: There was general agreement that the Cadmibel study was appropriate and that renal tubular dysfunction as measured by low molecular weight proteinuria is the critical effect of cadmium. However, there was uncertainty regarding which parameter was the best metric on which to do the modeling. Pre-meeting comments indicated that a later report on the Cadmibel study presented corrected values for calcium in urine that were about two-fold higher than those used in this file. Dr. Diamond indicated that the next most sensitive indicator of kidney effects is the NAG parameter. There was some concern about whether the 95th percentile cutoff points for the parameters represented a NOAEL or a LOAEL. If responses above this point are not biologically significant or do not result in clinical disease, then the cutoff point should be considered a NOAEL. A nephrologist should be consulted to determine if these responses are biologically significant.

There was also general agreement that a study of residents of the Kakehashi River Basin in Japan, known as the Ishikawa Prefecture Study (Ishizaki et al., 1989; Kido and Nogawa, 1993; Kido et al., 1991a,b; Kido et al., 1993; Nogawa et al., 1978; Nogawa et al., 1989; Nogawa et al., 1992; Nakagawa et al., 1993), should be used as a co-critical study with Cadmibel. An advantage of the Ishikawa Prefecture Study is that it measured

cadmium intakes. This study had higher levels of cadmium than the Cadmibel study; however, it also demonstrated more severe effects. Thus, it provides good support for the Cadmibel study.

Uncertainty Factors: A composite uncertainty factor of 10 was proposed.

Deficiencies in the database: An uncertainty factor of three was proposed for limitations in the database for developmental/reproductive effects. The reviewers questioned this and agreed that developmental effects are unlikely to occur at doses lower than those that cause kidney effects. Therefore, this factor is not needed. However, the document needs to provide better support for this decision.

Use of LOAEL: An uncertainty factor of three was proposed to account for the use of a minimal LOAEL. Reviewers were split on the issue of whether this factor was needed. Several reviewers felt that the endpoint was conservatively chosen and that the 95th percentile value of the normal range may not be equivalent to an effect level, and, thus, represented a NOAEL needing no uncertainty factor. Other reviewers felt that it was not possible to make a determination of whether the endpoints were a NOAEL or LOAEL until a nephrologist had been consulted.

Sensitive subgroups: No uncertainty factor was proposed for this area. However, one reviewer suggested a factor of three be used as not all parts of the population were included (e.g., young persons). However, other reviewers suggested that the study population did include appropriate sensitive subpopulations. There was no resolution on this issue.

Overall, the reviewers concluded that the total uncertainty factor could range from 1 to 10. Although there was some uneasiness expressed in adopting a total uncertainty factor of 1 (or even less than 10) due to mortality seen in the Nakagawa study at twice the estimated Cadmibel intakes. Before the total uncertainty factor is finalized, there should be additional explanation for not using the database uncertainty factor and a kidney specialist should be consulted on the health significance of the selected endpoint. A generic issue of what criteria need be met to accept a composite uncertainty factor of one needs to be discussed and resolved.

Panel Recommendation: The Panel made the following recommendations regarding revision of the cadmium RfD file:

* Include both the Cadmibel and the Ishikawa Prefecture studies as co-critical.
* Provide summary data tables (including standard deviations around doses, if possible) to clarify the findings of the studies.
* Renal tubular dysfunction as measured by low molecular weight proteinuria is the critical effect, but the document should more clearly tie this effect in with the changes in urinary cadmium excretion.
* Provide descriptions of the animal data to help explain the mechanism by which

cadmium is acting.
* Consult with a nephrologist regarding the biological significance of the parameters of kidney dysfunction.
* Provide additional support in the document for not using an uncertainty factor for database.

Acrylonitrile Presentation and Discussion

Susan Felter of Toxicology Excellence for Risk Assessment (TERA) presented the acrylonitrile assessment. Because of potential conflicts of interest Marvin Friedman and Matthew Bogdanffy participated in the discussion but were not polled for a recommendation. In addition, because of a conflict, Michael Dourson participated in the discussion but did not chair this portion of the meeting, nor was he polled for a recommendation. He turned the meeting facilitation over to Kenneth Poirier. See attached conflict of interest statement for more information.

The acrylonitrile (ACN) assessment was developed by TERA for Cytec Industries and The Acrylonitrile Group. Dr. Felter stated that the assessment utilized U.S. EPA methods and attempted to anticipate how EPA would assess this chemical. EPA has an existing assessment available on the Integrated Risk Information System (IRIS) with a classification of B1-probable human carcinogen and a quantitative estimate based on human occupational studies (O'Berg, 1980). Since several recent epidemiology studies, including the follow up to the O'Berg study, found no statistically significant excess of lung cancer mortality or incidence, TERA is proposing a new risk estimate based upon a rat bioassay. A preliminary version of this assessment was presented to the September 1996 Peer Review panel which discussed general issues related to cancer risk assessment. Below is a summary of the primary issues raised by the September panel along with the disposition of comments. (See the September 1996 meeting summary for more information about the results of the September peer review meeting.)

Disposition of Comments from September 1996 Panel

1. Hazard Characterization - Because U.S. EPA's 1996 proposed cancer guidelines are undergoing revision, the September panel agreed with TERA that a narrative description without a particular classification is appropriate if the description includes classifications from various agencies (e.g., IARC and EPA assessments). The current description needs to strengthen the link between the data and the conclusions. If inclusion of a "classification" is desired, it would be appropriate to use the EPA 1986 guidelines until the proposed 1996 guidelines are finalized. B2 seems an appropriate classification under the 1986 EPA guidelines.

TERA strengthened the weight-of-evidence discussion based on suggestions by the peer reviewers.

2. Epidemiological Studies - The assessment should provide more complete information

on the human studies in order to evaluate sensitivity. A sensitivity analysis should be conducted on the human studies and the data should be reviewed by an epidemiologist.

An epidemiologist was consulted and the discussion of the epidemiological studies was expanded. Confidence intervals and the results of power analyses were included when they were presented by the original authors, but they were not constructed specifically for the document. Further evaluation of the epidemiological studies is discussed below.

3. Tumor Types to Model from Rat Bioassay. The assessment should model both CNS tumors alone and combined incidence of tumor types found individually to be statistically significantly related to dose. A narrative to explain the differences in results should be included. Also, the assessment should show the proportion of benign to malignant tumors. Since there was high mortality, the assessment should be adjusted appropriately. Modeling of the CNS tumors should be the basis of the unit risk value.

As recommended, the individual animal data from Quast et al. (1980) were obtained and evaluated. Tumor incidence was determined for astrocytomas alone (benign and malignant). Tumor incidence was also determined for the combination of all tumors that showed a statistically significant response. In addition, tumor incidence was adjusted for early mortality by excluding animals that died before the time of the first tumor (and thus, were not at risk for developing tumors). Finally, the results of the modeling were presented as both the estimated dose that resulted in a 10% increase in tumors (ED-10) and the lower 95% confidence limit on that dose (LED-10).

Summary of Discussion and New Issues from December 1996 Panel

Hazard Characterization: The panel agreed overall with the hazard characterization statement and agreed that the narrative description is the most appropriate approach for expressing weight-of-evidence until U.S. EPA's 1996 cancer guidelines are finalized.

The decision to use animal data, rather than the occupational studies' results, required careful consideration. TERA solicited an in-depth review of this issue from one of the peer reviewers who is an epidemiologist. A power analysis of the human studies was conducted in order to determine if the epidemiology studies validate the findings in the animal studies. The analysis indicated that a 70% excess risk could have been detected by the existing human studies if the exposure had been approximately 3 ppm. Although the human studies had limited quantitative estimates of exposure, what data are available indicate that exposure was generally less than 3 ppm. Therefore, it is not likely that the human studies could have detected the smaller increase in risk (i.e., less than 70%) predicted by the model.

A second analysis suggests that the risks for total cancer predicted by the model at workplace exposure concentrations are below the detectability of the occupational epidemiology studies. For example, the observable range model predicts a 10% increase in risk for total cancer to occur at 30 ppm (using workplace exposure assumptions). The exposure concentration ranges in the epidemiology studies were below this level, and

10% risk is rarely detectable in occupational epidemiology studies. The ability of the epidemiological studies to detect brain cancer was discussed. It was stated that because brain cancer is rare in the human population (about 3% of human cancer), it is likely to be below the detectability of occupational cohort studies. The panel agreed that the findings in the epidemiological studies do not conflict with those of the animal studies and that the document should be revised to state that the "human data are not sufficiently powerful to rule out an association between exposure and cancer".

Quantitative Assessment: Overall, the panel agreed with the approach taken for the mortality adjustment and for the modeling of the tumor incidences. There was some discussion among the panel members on whether the document should present the results from both the astrocytomas and the combined tumors as well as both the ED-10 and LED-10. One reviewer recommended combining all tumor types because, in general, tumors do not show site concordance between laboratory animals and humans. However, other reviewers suggested that tumors in non-relevant tissues should not be included in the quantitative assessment. (It was acknowledged that there is no equivalent to the rat Zymbal gland in humans.) It was also noted that no tumor types other than the astrocytomas and Zymbal gland were consistently seen in the other animal studies. Tongue and small intestine were not found to be target organs in other bioassays. There was some concern that presenting such a variety of values may be confusing to risk managers. However, the panel concluded that the best approach is to present as much information about the potential variability of the value as possible and then to make a recommendation about which value should be used in risk assessment (the value based on astrocytomas alone). In addition, the reviewers suggested including information about the modeling such as the fit of the model, the effect of using different models, and the effect of using the 4% or 8% observed increase in tumor incidence rather than the estimated 10% increase. One reviewer also suggested including a graph that shows how well the model fits the data.

One reviewer questioned why both linear and non-linear approaches were not presented. Dr. Felter explained that ACN has potential genotoxic action, and EPA is therefore likely to use a linear model. Moreover, the data are currently insufficient to make the non-linear argument plausible; although research is ongoing to better elucidate the mechanism which appears to have both genotoxic and nongenotoxic components. (NOTE - The September 1996 panel did discuss this issue and recommended a linear approach.)

Panel Recommendation: The panel unanimously approved the ACN assessment for inclusion on the ITER database. The panel recommended that the file include a confidence statement. Dr. Felter drafted a confidence statement which the reviewers approved before the conclusion of the peer review meeting.

Chromium Presentation and Discussion

Deborah Proctor of the ChemRisk Division of McLaren/Hart presented the hexavalent chromium assessment. Because of a conflict of interest, Michael Gargas participated in the discussion, but was not polled for a recommendation regarding the chromium file. See attached conflict of interest statement for more information.

Presentation: A inhalation Reference Concentration (RfC) for hexavalent chromium particulates was proposed based on benchmark doses (BD) calculated from studies in rats by Glaser et al. (1985 and 1990). These studies exposed rats to an environmentally relevant chromate salt, measured very sensitive pulmonary endpoints, and reproducibly demonstrated a positive dose-response relationship. Data sets for 20 endpoints were evaluated for appropriateness to BD analysis and six were selected as reliable indicators of toxicity (four from Glaser et al., 1990 and two from Glaser et al., 1985). A range of RfC values was calculated based on benchmark doses. The lowest value of 0.34 ug/cu.m was proposed as the hexavalent chromium particulate RfC, representing the 95% lower confidence limit of the dose associated with a 10% increase in lactate dehydrogenase (LDH) levels in bronchiolar alveolar lavage fluid (BALF). The proposed composite uncertainty factor was 100.

Hazard Identification: The reviewers suggested that the document be revised to include a more complete discussion of the available human and animal studies in order to present a more complete picture of hexavalent chromium toxicity. The document also needs to clearly distinguish between the different forms of chromium and characterize the particle size for this RfC. A clear distinction is needed between chromic acid and soluble particles and the document needs to more explicitly state that it is for environmental exposures to hexavalent chromium dusts, and not exposures to chromic acid mists.

Much of the discussion focused on the spectrum of effects produced by hexavalent chromium exposure and whether the documentation package fully evaluated all possible effects in developing the RfC. For example, reviewers raised questions about whether upper respiratory, testicular and renal toxicity, which are known endpoints of hexavalent chromium exposure, were considered. Upper respiratory toxicity was of particular concern because of occupational studies where exposure to acid mists containing hexavalent chromium have indicated that perforated nasal septum is a common effect. Reviewers noted that one study included in the documentation package, Steffee and Baetjer (1965), examined the nasal septum but at only one dose. Also, one of the critical studies, Glaser et al. (1990) indicates that they examined the upper airway without showing the data. The panel recommended that the Glaser authors be contacted to determine if the raw data for the upper respiratory tract can be obtained. Review of this data, if available, may reduce the uncertainty associated with not knowing if the upper respiratory tract effects are the critical effect.

In addition, several reviewers noted that one of the critical studies, Glaser et al. (1985) demonstrated extrarespiratory immune effects (spleen cell response to sheep red blood cells and serum immunoglobulin) that might be significant effects. One reviewer noted that these effects could be indicative of pulmonary sensitization by chromium. The

reviewers suggested that an immunologist be consulted to determine whether these effects are biologically significant and should be considered as critical effects.

Pending resolution of the above issues, the reviewers evaluated the respiratory effects that were proposed as critical for the RfC; the panel had concerns about whether the most appropriate effect was selected. Several reviewers noted that the change in lung weight was a better endpoint because the model fits a better curve to these data and they are more robust. The panel questioned whether the endpoint selected, lactate dehydrogenase (LDH) in bronchiolar alveolar lavage fluid (BALF) is a biologically significant adverse effect. Ms. Proctor responded that they had considered the biological significance of all the endpoints selected for the modeling. Because the enzyme can only be detected in BALF when there has been lysis of cells, LDH was considered a good marker of the lung damage that occurs prior to development of fibrosis. LDH in BALF results in the lowest BD of the four endpoints. One reviewer noted that there was not a good fit of the model for this endpoint at the point where the dose-response curve bends. A better model would shift the curve to the right; therefore, the model used is health protective.

Critical Effect/Critical Study: Pending further investigations into immune effects and upper respiratory tract effects, the panel considered which of the lung effects modeled in the document should be considered as the critical effect. There was general agreement by the panel that all of the effects modeled were indicative of an inflammatory response and that the most appropriate approach was one that combined all effects. It was concluded that the mean of the benchmark doses was appropriate (reviewers noted that both an arithmetic and geometric mean give the same results in this case). The panel then discussed whether the LDH endpoint should be included in the mean because of the poorer model fit. It was noted that the mean of the benchmark doses for all four endpoints was 44.33 while the mean of the three endpoints without LDH was 37.25. Both these values round to 40. The panel recommended that the document include a discussion of the weaknesses of the various endpoints (i.e., poor model fit for LDH, change in lung weight possibly due to change in body weight). Also, the document should discuss the effect of particle size and define the RfC based on these deep lung effects as protective of exposures to very small particles only. There was discussion about whether the data from the 30-day recovery period should be used as the basis for the RfC. However, it was agreed that since the RfC is supposed to protect for continuous lifetime exposure, there would be no opportunity for recovery and thus the 30-day recovery data were not appropriate.

The benchmark dose calculations were reviewed and accepted after some discussion on the accuracy of the equation cited in the document. ChemRisk will check to confirm it is correctly presented.

Uncertainty Factors: A composite uncertainty factor of 100 was proposed.

Animal to human extrapolation: An uncertainty factor of three was proposed. Use of the Regional Deposited Dose Ratio (RDDR) accounts for the kinetic differences between rats and humans, but the pharmacodynamic interspecies differences are not addressed by the

dosimetric adjustment, necessitating the three-fold factor. The panel discussed whether data from other deep lung irritants could be used to quantify the toxicodynamic differences between animals and humans, thus reducing this factor even further. However, while this is an interesting topic for a research project, the panel concluded that this application of data to uncertainty factors is not practical at this time. An uncertainty factor of three was accepted.

Extrapolation from a subchronic study: An uncertainty factor of three for extrapolation from a subchronic study was proposed because the effects observed were considered to be precursors to chronic fibrosis. There was disagreement among the panel on whether a three or a ten was appropriate for this uncertainty factor. In support of a full ten factor, reviewers pointed to Figure 1 from Glaser et al. (1985) which indicates that chromium is still accumulating in the lung and kidney at the end of the 90-day exposure period, suggesting that exposure to even lower concentrations would eventually lead to accumulation of a critical concentration of chromium in the lung. Also, there is not enough information on how well subchronic studies predict chronic inflammation to warrant reducing the UF to three. In support of the three, are the data which show no increase in severity of effects between the 30-day and the 90-day exposures and the presence of an 18-month study (Glaser et al., 1984) which supports the findings of the 90-day study. Although there was not consensus, most reviewers felt that a value of three could be appropriate if it was well supported by a discussion of how well subchronic studies can predict chronic inflammation and if the results of the chronic study are incorporated.

Intraspecies variability: An uncertainty factor of ten was proposed. The panel agreed.

Database deficiencies: The panel also discussed the need for an uncertainty factor to account for gaps in the database. Reviewers noted that the document needs to fully describe all available data in order to warrant not using this uncertainty factor. In particular, the document needs to discuss data that might be available on upper respiratory tract toxicity and include any data obtained from Glaser. If this endpoint has not been adequately addressed, an uncertainty factor of three may be needed.

Panel Recommendations: The Panel made the following recommendations regarding revision of the chromium RfC file:

* Consult with an immunologist regarding the significance of the immune effects observed in Glaser et al. (1985).
* Investigate further the upper respiratory tract toxicity and attempt to obtain raw data from Glaser.
* Determine which deep lung effects should or should not be combined in order to use as basis of critical effect. Acknowledge that both the LDH and lung weight endpoints have weaknesses.
* Add a more complete discussion of all available animal and human studies, as well as ongoing research.

* Use the default uncertainty factor of 10 for use of a subchronic study, unless better support for reducing this to three can be provided. The uncertainty factors for intra- and interspecies are appropriate as proposed. An uncertainty factor for database may not be needed, but needs better justification.
* Provide a clearer distinction of the different forms of chromium the RfC is for and perhaps consider developing different RfCs for acid mists and dust containing hexavalent chromium.

Next Steps for Revision of Files

For cadmium and chromium files, the panel agreed that the sponsors should make the recommended revisions and send them to TERA. TERA will then distribute revisions to the panel and obtain consensus on the remaining issues by either letter review or conference call as necessary. If consensus cannot be obtained (or in the case of chromium, if the critical effect changes), then TERA will discuss with the sponsors the need for bringing the files back to another meeting. For ACN, the panel generally approved the confidence statement. However, Dr. Friedman and Dr. Erdreich will work with Dr. Felter to make minor revisions to the confidence statement and to the document. After these revisions, ACN can be placed onto the ITER database.

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