Admin

Hair Dye Epi

EXPERT PANEL MEETING
March 6-7, 2023

Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Jinqiu Zhu, PhD, DABT, ERT, DCST, CIR Toxicologist
Date: February 10, 2023
Subject: Draft Revised Hair Dye Epidemiology Document for Panel Review

Enclosed is an updated draft of the Expert Panel Resource Document – Hair Dye Epidemiology (*report_HairDyeDocument_032023*), and the transcripts of the discussion of the Resource Document at the previous Expert Panel meeting (*transcripts_HairDyeDocument_032023*). The previous draft was reviewed by the Panel at the March 2021 meeting. Comments received on the Resource Document from the Council (*PCPCcomments_HairDyeDocument_032023*), which had been submitted in Wave 3 at the March 2021 meeting, are included in the package, accompanying with the responses to these comments (*response-PCPCcomments_HairDyeDocument_032023*).

At the March 2021 meeting, the Panel agreed on the inclusion of 12 additionally-identified studies (including one study submitted in Wave 2), and maintained the conclusion that the available epidemiology data did not provide sufficient evidence for a causal relationship between personal hair dye use and cancer. The Panel further requested Table 1 in that document be reorganized to cover all studies and include more study details. Accordingly, previous Table 1 has been split into three separate tables based on the type of study (i.e., cohort, case-control, and meta-analysis), which cover all studies listed in the main text with one exception (reference 75 is a cross-sectional study). Meanwhile, more detailed information of each study has been included, such as study population, diagnosis/publishing period, hair dye exposure patterns, ranking of the study (Rollison scale), adjudgment of confounder, as well as more risk ratio data resulted from analysis stratified by race, gender, hair dye type, duration and frequency of use, etc. While it was not applicable to incorporate all data of the studies into the tables, particular attention was given to the relevant risk estimates associated with permanent dark dyes, long duration and high frequency of hair dye applications. For some studies, the authors have made specific clarifications on their findings (e.g., increased NHL risk was limited to women who used dark color or intense tone permanent hair dyes before 1980); such information was also noted in the tables for the Panel's consideration.

The order of the studies under each subsection of the cancer type has been re-organized in accordance with the study design and chronological sequence. Following the re-organization, more information has been incorporated into several studies. Data that the Panel did not review previously in detail has also been highlighted therein for the Panel's consideration.

The Panel requested continued monitoring of upcoming epidemiological data on the link between personal use of hair dyes and cancer risk. Since March 2021, six new epidemiological studies, including one meta-analysis study, one case-only study, one case-control study, and three prospective cohort studies, have been discovered. These additional studies (plus one case-control study submitted in Wave 2 at March 2021 meeting) are incorporated herein, and highlighted in yellow, for the Panel's consideration. Please also note, as suggested by the Panel, when studies were already included in a meta-analysis, they would not particularly be referenced or presented in the document. As it is not applicable to incorporate all details of each involved study in the table, readers are always encouraged to refer to the original meta-analysis paper for more information on characteristics of included studies, such as inclusion and exclusion criteria, weight of each study in the final statistical analysis, the heterogeneity test among different trials, risk of bias, strengthens and limitations of study, etc.

Two case studies addressing the safety assessment of a specific hair dye ingredient (i.e., Basic Blue 124) or trace contaminant (4-Aminobiphenyl) in Phenylenediamine (PPD) ingredient were also incorporated and highlighted in the Background section. These studies demonstrated utilization of the Threshold of Toxicological Concern (TTC) approach or Margin of Safety (MoS) calculation to examine cancer risk that is associated with specific ingredient/impurity exposure during hair dye applications.

The Panel should review this Document, especially noting the data presented in the new studies as well as the additional information incorporated in the reorganized tables. If this Document is in agreement with their thinking, it should be finalized and used to replace the version currently posted on the Findings & Resources Documents page (https://www.cir-safety.org/cir-findings). If the Document is not considered to be ready for finalization, specific needs/edits therein should be made evident.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: March 9, 2021

SUBJECT: Expert Panel Resource Document: Hair Dye Epidemiology (draft prepared for the March 11-12, 2021 meeting of the Expert Panel for Cosmetic Ingredient Safety)

The Personal Care Products Council respectfully submits the following comments on the Expert Panel Resource Document: Hair Dy Epidemiology.

Key Issue

Page 8, the Sisters study - The 45% higher breast cancer risk in black women was for subjects reporting use of permanent hair dye in the 12 months before study enrollment. However, as presented in Table 3 of the study, no significant association is seen between permanent hair dye use and breast cancer risk when durations of use ('years of personal use') are considered. The adjusted hazard ratio for black women reporting >5 years of permanent hair dye use is 0.97 (95% CI 0.70,1.34); for those reporting <5 years the HR is 1.08 (0.77,1.52). The adjusted hazard ratio in white women reporting >5 years of permanent hair dye use is 1.06 (0.97,1.16); for those reporting <5 years, the HR is 1.10 (0.97,1.24).

Additional Considerations

Background – The first sentence about the IARC review should also mention animal studies, as animal studies are mentioned later.

Study Summary – Please delete the word "recently" in the summary of the new prospective study (reference 8), as it will not apply a few years from now.

Lymphoma and Leukemia – "DCBCL" should be revised to "DLBCL"

In the summary of reference 27, please clarify if the children, or the parents of the children with leukemia used hair dyes.

In the summary of reference 18 in both the text and table it states: “Multivariable regression analysis indicated that parents use of hair dye during breastfeeding..” Did the really indicate “parents” or should this just be “mothers”?

Page 6, 1st (incomplete) paragraph – “…when all studies were combined, the OR value was 1.14 (95% CI: 1.01 - 1.29), indicating that the risk of NHL in a high population of hair dye users was 14%.” This statement needs re-wording – what is high, the number of hair dye users, or their use of hair dyes?

In the summary of reference 29, please revise the following sentence: “The results suggested that people who used more than 20 years of hair dye had increased risk of NHL.” To “The results suggested that people who used hair dyes for more than 20 years had increased risk of NHL.”

Glioma – Please revise: “cohort studies of personal was conducted to investigate the hair dye use and the incidence of gliomas” to “cohort studies were conducted to investigate personal hair dye use and the incidence of gliomas”

Expert Panel Resource Document: Hair Dye Epidemiology March 6-7th, 2023 Panel Meeting – Jinqiu Zhu	
Comment Submitter: Personal Care Products Council Date of Submission: 3/9/2021	
Comment	**Response/Action**
Key Issue –Page 8, the Sisters study - The 45% higher breast cancer risk in black women was for subjects reporting use of permanent hair dye in the 12 months before study enrollment. However, as presented in Table 3 of the study, no significant association is seen between permanent hair dye use and breast cancer risk when durations of use ('years of personal use') are considered. The adjusted hazard ratio for black women reporting >5 years of permanent hair dye use is 0.97 (95% CI 0.70,1.34); for those reporting 5 years of permanent hair dye use is 1.06 (0.97,1.16); for those reporting <5 years, the HR is 1.10 (0.97,1.24).	Such data were added into the main text and the Table 1.
Background – The first sentence about the IARC review should also mention animal studies, as animal studies are mentioned later	Addressed
Study Summary – Please delete the word "recently" in the summary of the new prospective study (reference 8), as it will not apply a few years from now.	Addressed
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Page 6, 1st (incomplete) paragraph – "…when all studies were combined, the OR value was 1.14 (95% CI: 1.01 - 1.29), indicating that the risk of NHL in a high population of hair dye users was 14%." This statement needs re-wording – what is high, the number of hair dye users, or their use of hair dyes?	Addressed
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EXPERT PANEL FOR COSMETIC INGREDIENT SAFETY

Expert Panel Resource Document

Hair Dye Epidemiology

03/2023 - DRAFT

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This resource document was prepared by Jinqiu Zhu, Ph.D, D.A.B.T., E.R.T, D.C.S.T., CIR Toxicologist.

BACKGROUND

Hair dyes may be broadly grouped into oxidative (permanent) and direct (temporary or semi-permanent) dyes.[1,2] The oxidative dyes comprise an admixture of precursors, couplers, and developers which result in the active dye; while direct dyes consist of preformed colors. Oxidative hair dyes, which represent more than 70% of the market, cause lasting chemical changes in the hair shaft. The color/shade achieved on the hair depends on the ingredient identities, concentrations, and duration of exposure.[3] Dark dyes tend to contain the highest concentrations of the coloring ingredients, whereas light shades (blond) contain lower concentrations. In contrast to permanent and semi-permanent dyes, temporary dyes cover the surface of the hair but do not penetrate into the hair shaft. During hair dye applications, some chemicals can be absorbed in small amounts through the skin or inhaled from fumes in the air. Use of such hair dye constituents may result in incidental systemic exposures and pose health risks through photo-oxidation or direct free radical mechanisms.[4] Epidemiology studies that seek to determine associations, if any, between hair dye use and disease, provide broad information and have been considered by the Expert Panel for Cosmetic Ingredient Safety (Panel). However, these studies do not specifically address the safety of individual hair dye ingredients.

The Panel reviews new epidemiological studies addressing the personal use of hair dyes as these studies become available. Tables 1-3 summarize the epidemiology data according to study design (case-control, cohort, or meta-analysis) across different cancer types. Occupation as a hairdresser, barber, or cosmetologist/beautician involves exposures to multiple products used during work, making it difficult to use the results of such studies to inform the assessment of the risk, if any, associated specifically with hair dyes. Accordingly, such studies are not summarized here.

The Panel considers that epidemiological studies, when based on better information about exposure, can provide more useful findings than other such studies. According to one study, exposure assessments in hair dye epidemiology studies ranged from minimal information (e.g., ever/never use) to subject-recalled information on type, color, duration and frequency of use.[5] In this study, a scale from + to ++++ has been developed to rate the quality of hair dye exposure assessments in hair dye epidemiology studies, as shown below. Such scale (referred to as Rollison et al. (2006) scale in the document) was used to score the studies that are summarized in Tables 1-2:

+: Assessed ever/never use;
++: Assessed the type of hair dye, *or* dye type plus dye color or duration, *or* with information on two or three other factors (color, frequency, duration), but no information on type;
+++: Assessed dye type, color, *and* frequency *or* duration of use;
++++: Assessed all four critical aspects: hair dye type, color, duration, and frequency of use.

Hair dyes comprise a range of chemicals, depending on the type and color. The US National Toxicology Program (an interagency program of the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the US Food and Drug Administration (FDA)) classifies some chemicals that are or were used in hair dyes as "reasonably anticipated to be human carcinogens," while it has not classified the potential of hair dyes to cause cancer (i.e., identified a possible hazard without characterizing risk).[1] The International Agency for Research on Cancer (IARC) working group assessed carcinogenic effects of diverse hair dyes constituents in animal studies, and further reviewed pertinent epidemiology studies and observations on various cancer types, such as breast, bladder and hematological cancers.[6,7] The working group concluded that the animal studies provided limited evidence for the carcinogenicity of hair colorants, and the data are of insufficient quality, consistency, or statistical power to establish the presence or absence of a causal link between personal use of hair dyes and cancer. Based on a lack of evidence from studies in people, IARC considers personal hair dye use to be "not classifiable as to its carcinogenicity to humans" (classified as Group 3).[1,8] In addition, occupational exposure during work as a hairdresser, barber, or beautician was assessed. People who work around hair dyes regularly are likely to be exposed more than people who just dye their hair on occasion. The working group found that exposures from these occupations are "probably carcinogenic to humans" (classified as Group 2A)[9] based on limited evidence of increased risk for bladder cancer in hairdressers and barbers. (The evidence for other types of cancer is considered mixed or inadequate.) Equivocal epidemiological findings were reported regarding the cancer incidence among hairdressers.[4,10] However, occupational safety is outside the scope of the work of the Panel.

Studies evaluating the exposure to compounds in the context of chemical mixtures during hair dye use allows for an assessment of the cumulative cancer risk. For instance, a recent risk assessment was performed to examine the risk of bladder cancer in humans from exposure to 4-aminobiphenyl (4-ABP) in consumer use of hair dye.[11] 4-ABP is classified as a human bladder carcinogen by IARC and can be present as a trace contaminant in *p*-phenylenediamine (PPD) (an oxidative hair dye ingredient). 4-ABP concentrations in consumer hair dyes can range from 0.15 (below the limit of detection) to 8120 ppb, which may result in maximum daily systemic exposure doses (SEDs) from 0.05 to 3000 pg/day (in consideration of dermal application of hair dye). The Office of Environmental Health Hazard Assessment (OEHHA) has established the no-significant-risk-level (NSRL) of cancer risk for 4-ABP at 0.03 µg/day.[12] A margin of safety (MoS) was calculated as the ratio of NSRL to the SED, based on a conservative model assuming that a consumer uses permanent hair dye on a daily basis. The calculated MoS ranged from 10 to 570,000, which suggested there was no indication of increased cancer risk in humans from exposure to 4-ABP during consumer hair dye applications. (NSRL is defined as the daily intake level posing a 10^{-5}

lifetime risk of cancer; an MoS of greater than 1 indicates an exposure scenario with a low likelihood of increased risk.) Furthermore, consumer use of oxidative hair dye is considerably less frequent than every day; thus, such MoS can be considered quite conservative.

The Threshold of Toxicological Concern (TTC) approach may serve as a pragmatic tool for safety assessment of hair dye ingredients with low consumer exposure (proposed intermittent consumer exposure scenario, i.e., every 4 - 6 weeks for oxidative hair dyes and every 2 - 3 weeks for direct hair dyes).[13] In a case study taking direct hair dye Basic Blue 124 as an example, a potential maximum consumer exposure was derived as 0.32 µg/kg body weight (bw) for a 60 kg person, based on in vitro skin penetration rate at 0.033 µg/cm^2 (mean +1 SD) and exposure of 19.1 µg per hair dying event. Such maximum acute consumer exposure is about 7-fold below the TTC value for the Cramer Class III (i.e., chemicals with structures that permit no strong initial impression of safety and may even suggest a significant toxicity) threshold value of 2.3 µg/kg bw/day as defined by Yang et al. (2017).[14] Additional refinement is possible because of the intermittent consumer exposure scenario in real-life situations (consumer exposure at maximum every 2 - 3 weeks for a direct hair dye use).

The studies herein result in either an odds ratio (OR) or a relative risk (RR, also called risk ratio), two similar but not synonymous terms. An OR represents the odds that an outcome (e.g., cancer) will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure, whereas a RR is a measure of the risk of a certain event happening in one group compared to the risk of the same event happening in another group.[15-17] In epidemiological cancer research, ORs are most often used in case-control (backward looking) studies, and RRs are used in prospective (forward looking) studies, such as cohort studies and clinical trials. OR can also be used in cross-sectional and cohort study designs as well (with some modifications and/or assumptions). An OR or RR of 1 means there is no difference between two groups in terms of risk following a particular exposure; an OR or RR < 1 means that the exposure may reduce the risk of cancer (possibly protective), while OR or RR > 1 means the exposure may increase the risk of cancer (possibly causal). Broadly equivalent to RR, hazard ratio (HR) is applied when the risk is not constant with respect to time. It uses information collected at different times to simply compare two hazards.[18] A HR not equal to 1 indicates that two events are not occurring at an equal rate, and the risk of an event in one group is different than the risk of an event in another at any given time interval. The 95% confidence interval (CI) is used to estimate the precision of the OR or RR. If a 95% CI for the relative risk includes the null value of 1, then there is insufficient evidence to conclude that the groups are statistically significantly different.

Many oxidative dye products were reformulated in the early 1980s to eliminate ingredients that may promote tumors according to experimental bioassay studies.[1,19] Therefore, studying exposure to hair dyes from decades ago may be different from current exposures (e.g., whether it took place before or after 1980). However, some meta-analyses may involve weighted studies that contained case subjects who started to use hair dyes before 1980 and were positively associated with cancer risks. Note in many studies identified, hair dye use was just one of many exposure variables on which information was collected. In addition, hair dye formulations may also differ based on the region of the world in which they are produced and sold. Hence, the specific product used and the timing of use should be better considered. Strengths of the epidemiologic studies warrants evaluation of a variety of populations. The baseline cancer risk and environmental diversity of the locations where epidemiological studies were conducted should also be considered.[20] Thus, considering the confounding factors in some studies and the incongruent scope of many exposure assessments, adequate characterization of exposures and exposure-sources is a major methodological challenge to evaluating hair dye epidemiology relevance.

The following provides a brief summary of many relevant epidemiological studies that have been published since about 2010, as well as older epidemiological studies that were included in comprehensive reviews, such as that published by the IARC in 2010.[7] The Panel intends to continue monitoring epidemiological data on the link between personal use of hair dyes and cancer risk, and the conclusion of this resource document will be re-evaluated based upon the new information on a regular period basis.

STUDY SUMMARY

Multiple Cancer Type Measurements

A prospective cohort study was performed to comprehensively investigate the relationship between cancers in US women and use of permanent hair dye.[21] The participants included 117,200 women (30 - 55 years old) enrolled in the Nurses' Health Study who were free of cancer and reported personal use of permanent hair dyes at baseline (1976). During 36 years of follow-up (between 1976 - 2012), a total of 20,805 solid cancers and 4860 cancer related deaths were documented. Data collection on permanent hair dyes use were detailed in duration of use (non-user, < 5 years, 5 - 9 years, ≥ 10 years); frequency of use (non-user, every ≥ 5 weeks, every 1 - 4 weeks); cumulative dose (non-user, 1 - 99 times, 100 - 199 times, ≥ 200 times); age at first use (non-user, < 30 years, ≥ 30 years); and time since first use (non-user, < 30 years, ≥ 30 years). This hair dye exposure assessment was +++ on the Rollison et al. (2006) scale. Overall, no association was identified between ever-users of permanent hair dyes and risk of solid cancers under investigation (HR 0.98, 95% CI: 0.96 - 1.01; n = 20,805). Specifically, there is no significant increases in risk of the following cancer types: cutaneous squamous cell carcinoma (HR 1.00, 95% CI: 0.93 - 1.09; n = 2792), bladder cancer (HR 1.05, 95% CI: 0.90 - 1.24; n = 596), melanoma (HR

1.01, 95% CI: 0.89 - 1.14; n = 1198), breast cancer (HR 1.02, 95% CI: 0.98 - 1.07; n = 9252), brain cancer (HR 0.72, 95% CI: 0.56 - 0.93; n = 277), colorectal cancer (HR 1.05, 95% CI: 0.97 - 1.14; n = 2394), kidney cancer (HR 1.03, 95% CI: 0.85 - 1.23; n = 477), lung cancer (HR 0.9, 95% CI: 0.87 - 1.01; n = 2623), ovarian cancer (HR 1.09, 95% CI: 0.97 - 1.22; n = 1215), and all hematopoietic cancer (HR 1.00, 95% CI: 0.91 - 1.10; n = 1,807); while basal cell carcinoma risk was slightly increased for ever-users (HR 1.05, 95% CI: 1.02 - 1.08; n = 22,560). An increased risk of Hodgkin lymphoma was also observed for women with naturally dark hair (HR 3.89, 95% CI: 1.61-9.40; n = 24). When basal cell carcinoma and cutaneous squamous cell carcinoma were excluded from analysis, the overall HR for all cancers under investigation was 1.00 (95% CI: 0.96 - 1.05). Additionally, ever-users did not have an increased risk of cancer related deaths (HR 0.96, 95% CI: 0.91 - 1.02). Interestingly, self-administered questionnaires indicated hair dye ever-users were more likely to be smokers and consumed more alcohol than those reporting no permanent hair dye use. But the authors also claimed that the generalizability of current findings is limited to white US women and might not extend to other populations; cohort was not randomly sampled from US women, enrolled only nurses and more than 96% of the women had European ancestry.

In a prospective cohort study conducted in the framework of the Shanghai Women's Health Study, a total of 70,366 women completed a baseline survey between 1996 and 2000 and were followed up to 2005.[22] In the sample, 29,076 women reported ever using hair dye (use ranged from 1 to 52 years) and a total of 2437 women were diagnosed with cancer during follow-up. Hair dye users had a median age of 51 years, and a mean of 3.8 years of use. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale. Generally, no evidence of an association was identified between personal use of hair dye and cancer risk. Compared with no use, ever-users had an overall cancer risk of 0.89 (95% CI: 0.82 - 0.97, n = 2437), adjusted by age, education, and smoking. No significant association was observed for common cancers, including cancers of the breast (RR 0.93, 95% CI: 0.78 - 1.09; n = 592), colorectum (RR 1.04, 95% CI: 0.84 - 1.28; n = 390), lung (RR 0.81, 95% CI: 0.62 - 1.09; n = 249), stomach (RR 0.90, 95% CI: 0.66 - 1.21; n = 188), uterine (RR 1.10, 95% CI: 0.77 - 1.58; n = 125), ovarian (RR 0.89, 95% CI: 0.59 - 1.35; n = 100), thyroid (RR 0.42, 95% CI: 0.25- 0.69; n = 88), kidney (RR 1.11, 95% CI: 0.64 - 1.92, n = 54), brain cancer (RR 0.96, 95% CI: 0.56 - 2.35; n = 39), hematopoietic (RR 0.89, 95% CI: 0.59 - 1.35; n = 99), or their subtypes, including non-Hodgkin lymphoid neoplasms (NHL) (RR 1.09, 95% CI: 0.61 - 1.92; n = 51), multiple myeloma (RR 0.84, 95% CI: 0.31 - 2.27; n = 18), and leukemia (RR 0.68, 95% CI: 0.31 - 1.51; n = 29). No relation was documented between duration of hair dye use (non-user vs. 1 - 2 years vs. 3 - 4 years vs. 5 - 9 years vs. ≥ 10 years) and risk of cancer. Stratification by menopausal status indicated no association between breast cancer and hair dye use in either pre- or post-menopausal women.

A perspective cohort study included 573,369 women who were enrolled in Cancer Prevention Study II (CPS-II) of American Cancer Society in 1982.[23] The participants aged ≥ 30 years, with a median age of 56 years, and were followed up to 1989. The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale. Information collection on hair dye use included duration (no use, 1 - 9 years, 10 - 19 years, ≥ 20 years), and dye colors (blond, red/auburn, brown, black, or other dye). Models adjusted for age, race, and smoking. Overall, permanent hair dyes showed decreased risk of all fatal cancers combined (RR = 0.93, 95% CI = 0.89 - 0.98), and of urinary system cancers (RR = 0.65, 95% CI = 0.49 - 0.87). Note this study relied on mortality rather than incidence to define disease. Specifically, no increase in risk of any type of the following cancer types: breast (RR 0.95, 95% CI: 0.83 - 1.08), bladder (RR 0.56, 95% CI: 0.32 - 0.99), brain and other nervous system (RR 0.85, 95% CI: 0.67 - 1.09), digestive system (RR 0.94, 95% CI: 0.85 - 1.03), respiratory system (RR 1.00, 95% CI: 0.91 - 1.11), oral cavity and pharynx (RR 0.61, 95% CI: 0.32 - 1.14), and all hematopoietic cancer (RR = 0.94, 95% CI = 0.80 - 1.10). Women who had used black hair dyes for 20 years (0.6% of women hair dye users) or more had an increased risk of fatal NHL (RR = 4.37, 95% CI = 1.3 - 15.2; n = 3) and multiple myeloma (RR = 4.39, 95% CI = 1.1 - 18.3; n = 2). However, it should be noted the number of cases was very small, and thus the statistical power of these sub-analyses was limited.

One meta-analysis identified 79 studies, carried out in 11 countries, to examine the association between personal use of hair dyes and relative risk of several types of cancer.[24] Retrieved studies were published in any language between 1966 - 2005, with special focus on extensive use (> 200 lifetime episodes) of permanent dyes, and excluded those dealing with occupational exposure. Study-specific relative risks were weighted by the inverse of their variance (study heterogeneity) to obtain fixed- or random-effects pooled estimates. The pooled RR for ever-users of hair dyes was 1.06 (95% CI, 0.95 - 1.18) for breast cancer (14 studies), 1.15 (95% CI: 1.05 - 1.27) for hematopoietic cancers (40 studies), and 1.01 (95% CI: 0.89 - 1.14) for bladder cancer (10 studies), as summarized below under divided section for specific type of cancer. Some cancers were examined by only 1 or 2 studies. The pooled RRs of the 2 studies available were 1.83 (95% CI: 1.16 - 2.89) for brain tumors, 1.71 (95% CI: 1.15 - 2.53) for ovarian cancer, 0.74 (95% CI: 0.51 - 1.07) for skin cancer, and 0.89 (95% CI: 0.53 - 1.9) for cervical cancer. The single case-control study on cancers of salivary glands showed the OR was 2.3 (95% CI: 0.9 - 6.2) and 3.5 (95% CI: 0.9 - 12.8) for hair dye use ≤ 15 years or >15 years, respectively.[25]

Breast Cancer

A national prospective cohort Sister Study was carried out to examine the association between hair dye and straightener use and breast cancer risk by ethnicity.[26] Study participants were 46,709 women aged 35 - 74 and came from all 50 states in the U.S. and Puerto Rico. Subjects included women who did not have a breast cancer diagnosis at the time of study recruitment (between 2003 - 2009) and who had 1 or more sisters diagnosed with breast cancer. This hair dye exposure

assessment was ++++ on the Rollison et al. (2006) scale. Compared to nonuse, use of permanent dye was associated with 45% higher breast cancer risk in black women (HR 1.45; 95% CI: 1.10 - 1.90, n = 102), and 7% higher risk in white women (HR 1.07; 95% CI: 0.99 - 1.16, n = 1338). A higher breast cancer risk was also observed in light-colored dye (HR 1.12; 95% CI:1.02 - 1.23, n = 713), compared to dark-colored dye (HR 1.08; 95% CI: 0.98 - 1.19, n = 683). Non-professional application of semi-permanent dye to others was associated with breast cancer risk (HR 1.28, 95% CI: 1.05-1.56; n = 105), while association was not found for non-professional application of permanent dye to others (HR 0.99, 95% CI: 0.85-1.15; n = 188). However, no significant association was seen between permanent hair dye use and breast cancer risk in both white and black women when the analysis was stratified by durations of use: HR was 0.97 (95% CI: 0.70 - 1.34, n = 59) and 1.06 (95% CI: 0.97 - 1.16, n = 1177) for duration of use ≥ 5 years in black women and white women, respectively. In addition, semi-permanent dye and temporary dye use was not associated with risk. While the findings of present study suggested higher breast cancer risk is associated with personal use of permanent dye, especially among black women, limitations of the study design and analysis need to be considered before jumping to a general conclusion: i) women were recruited to the study because they had a sister with breast cancer (i.e., all subjects in the current study had a significant risk factor of breast cancer), so the conclusions cannot be extended to the wider population; ii) since older age is a strong risk factor for breast cancer, other researcher argued the findings of this study have not been adjusted for age;[27] and iii) confounding factors warrant further examination when adverse effects of endocrine disrupting chemicals (EDCs) need to be investigated (women who use hair dye more commonly generally also use more cosmetics, which contain EDCs), while exposure to EDCs is largely related to environmental and nutritional factors. None of these effect modifiers has been addressed in the present study. Social or cultural factors may also associate with patterns in both hair dye usage and breast cancer risk, especially between black and white women.[28]

Based on the same Sister Study cohort described above, the association between adolescent use of hair dye (subjects reported their hair dye use at ages of 10 to 13 years, n = 47,522) and breast cancer risk were further investigated.[29] Information on hair dye type (permanent, semi-permanent, temporary) and frequency of use (sometimes or frequently) were collected. The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale. Over 10 years follow-up, 3380 incidences of breast cancer cases were diagnosed. Adolescent use of either permanent or semi-permanent hair dye was uncommon (< 3%), and hair coloring products were not associated with breast cancer risk overall (HR 0.97, 95% CI: 0.78 - 1.20) or by menopausal status. With consideration of race/ethnicity, permanent dye use was associated with a higher risk among black women (HR 1.77, 95% CI: 1.01 - 3.11); however, it should be noted such analysis was based on a small number of exposed cases (n = 13); in comparison, among white women (exposed cases n = 70), the association between hair dyes use and incident breast cancer was not identified (HR 0.93, 95% CI: 0.74 - 1.18). In addition, black women who reported using permanent hair dye during adolescence reported also using permanent hair dye in the 12 months prior to study baseline (n = 10 of 13 exposed cases); thus, the authors stated they could not reliably estimate the association of only using permanent hair dye during adolescence.

A case-control study was conducted, including 191 breast cancer patients interviewed in a hospital in 1975 - 1976 in the UK, with 561 sex, age (within three years), marital status, and social class matched controls.[30] The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. Seventy-three (73) cases and 213 controls had used permanent or semi-permanent hair dyes, giving an RR of 1.01 (95% CI was not available). There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or over nine years (RR = 0.95) before diagnosis.

A case-control study consists of 50 breast cancer patients at a cancer treatment center with 100 hospitalized controls in London, Ontario, and 35 breast cancer cases with 70 neighborhood controls in Toronto, Ontario.[31] The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. The RRs for breast cancer from use of permanent hair dyes (at any time) were 1.30 (95% CI: 0.60 - 2.50) in London and 1.10 (95% CI: 0.50 - 2.40) in Toronto. Further statistical analyses, allowing for smoking habits, family history of cancer and age at first birth, showed no significant relationship between hair-dye use and breast cancer incidence.

A hospital-based case-control study was performed among 398 breast cancer patients at a screening center between 1977 and 1981 in New York City (NYC), with 90 randomly selected controls.[32] Information collected for hair dye use included type (permanent, semi-permanent, temporary), dye color (light, medium, dark), duration (different periods of reproductive life) and frequency of use (no-use, 1 - 9 times, 10 - 49 times, 50 - 149 times, 150 - 1825 times). The evaluation of hair dye exposure was a ++++ on the Rollison et al. (2006) scale. The OR for breast cancer from ever-use of hair dyes was 0.80 (95% CI: 0.60 - 1.10). There was also no evidence of a trend in risk with increasing number of hair dye uses (38% of the subjects had used hair dye at least 100 times, while 77% had used hair dyes at least once). An analysis of breast cancer risk in women working as beautician for ≥ 5 years was also performed. Although personal hair dye use was unrelated to breast cancer risk, the OR for beauticians was 3.00 (95% CI: 1.10 - 7.80).

A population-based case-control study in Finland recruited a total of 6567 breast cancer patients diagnosed between 2000 and 2007 and 21,598 age-matched controls.[33] The evaluation of hair dye exposure was a +++ on the Rollison et al. (2006) scale. The recruitment of patients was based on a nationwide cancer registry covering almost 100% of solid tumors. The exposure of primary interest was the use of hair dyes with detailed information on the cumulative lifetime number of hair

dye episodes, age at first use, and the types of dyes used. When calculating ORs, potential confounding factors, namely parity, age at first birth, family history of breast cancer, menarche age, use of hormonal contraceptives, physical activity, alcohol use, body mass index (BMI), and education, were included in a stepwise regression model. Bias-adjusted ORs were calculated as well. A large proportion of women reported ever-use of hair dye products, with rates increasing from 84% in women born before 1950 up to 92% in women born in or after 1960. The odds of breast cancer were significantly increased when comparing ever vs never users (OR 1.23, 95% CI: 1.11 - 1.36). Early age at first dye (20 -29 years) was associated with higher odds of breast cancer when compared to late age at first dye (40 years or later) (OR 1.14, 95% CI: 1.05 - 1.25). When considering ever-use vs. non-use, the ORs were increased with all the different types of hair dyes, the highest estimates being obtained for women who reported to have used temporary and semi-permanent dyes, ORs being 1.32 (95% CI: 1.16 - 1.52) and 1.31 (95% CI: 1.17 - 1.46), respectively. Latency of effect was suggested by the fact that the OR for cumulative hair dye use was the highest among women born between 1950 and 1959. When considering the cumulative number of hair dye episodes, the OR ranged from 1.07 (1 - 2 dye episodes) to 1.28 (10 - 34 dye episodes) and 1.31 (35 - 89 dye episodes), and then decreased to 1.25 (≥ 90 dye episodes). The ORs did not change when smoking was included in the multivariate analysis.

A hospital-based case-control study of breast cancer was conducted on 1052 women in Iran.[34] The evaluation of hair dye exposure was + on the Rollison et al. (2006) scale. There were 526 newly diagnosed breast cancer cases, with 526 age-matched controls randomly selected in Namazi Hospital between November 2014 and March 2016. The study showed that multiple factors were associated with the risk of breast cancer, such as hair coloring, age at first delivery, stress, and smoking. The OR of breast cancer from hair dye use on a regular basis compared to no use was 1.93 (95% CI: 1.41 - 2.62). However, the design of the study was not able to confirm a causal association between any investigated variables and breast cancer.

In a population-based case-control study involving African American and European American women from the Women's Circle of Health Study (WCHS), conducted in the metropolitan NYC area and ten counties in New Jersey (NJ), breast cancer cases were identified by multiple sources, including hospital charts and NJ cancer registry.[35] Recruitment in NYC was conducted between 2002 to 2008, while recruitment in NJ finished between 2006 to 2014. The subjects were 1508 African American and 772 European American cases (52 ± 10.7 and 52.0 ± 10.0 years old, respectively) and 1290 African American and 715 European American age- and county-matched control subjects (50.9 ± 10.3 and 49.8 ± 8.7 years old, respectively). The evaluation of hair dye exposure was ++++ on the Rollison et al. (2006) scale. Final OR estimates were adjusted by age, education, BMI, family history of breast cancer, and oral contraceptive use. In the control group, about 30% of African Americans and 58% of European Americans reported regular use of hair dyes. Overall, ever-use of hair dyes and duration of use were not significantly associated with increased cancer risk in both African Americans (OR 1.12, 95% CI: 0.95-1.32) and European Americans (OR 1.07, 95% CI: 0.86-1.32). Among African Americans, an increased risk of breast cancer was documented for the use of dark hair dye shades, and for salon application of dyes, adjusted OR being 1.52 (95% CI: 1.21 - 1.91) and 1.26 (95% CI: 1.00 - 1.58), respectively. In European Americans, an increased risk was documented for dual use of relaxers and hair dyes with OR 2.40 (95% CI: 1.35 - 4.27), the wide CI reflecting the limited number of exposed women. When considering the estrogen receptor (ER) status of cancer, the risk of estrogen positive breast cancer was increased in African Americans with a higher frequency of hair dye use (OR 1.36, 95% CI: 1.01 - 1.84) and in European Americans with the use of dark hair dye shades (OR 1.54, 95% CI: 1.01 - 2.33). These differences in risk profile between African Americans and European Americans are not easy to reconcile. They may reflect different patterns of use, or represent chance effects due to multiple testing.[20] Replication of results by an independent study is needed. Ideally, such a study should be able to ascertain the type of hair dye product used and its timing of use.

In the following case-only analysis conducted by the same research group, 2998 women with breast cancer enrolled in both WCHS and Women's Circle of Health Follow-up Study (WCHFS), were included to examine whether certain characteristics of use of hair dyes and relaxers were associated with more aggressive tumor features, such as larger tumor size, higher tumor grade, positive lymph node status, etc.[36] The participants (2227 African Americans and 771 European Americans) were recruited from 2001 to 2018, with the mean age 53.3 ± 10.6 years at diagnosis. Compared to salon application of permanent hair dye, home kit and combination application (both salon and home kit use) were associated with increased odds of poorly differentiated tumors. This association was consistent among African Americans (home kit: OR 2.22, 95% CI: 1.21 - 5.00; combination: OR 2.46, 95% CI: 1.21 - 5.00), but not European American women (home kit: OR 0.90, 95% CI: 0.45 - 1.81; combination: OR 2.05, 95% CI: 0.94 - 4.47). In the overall study sample of breast cancer cases (both African American and European American women), home kit OR was 1.41 (95% CI: 0.87 - 2.29), and combination OR was 2.27 (95% CI: 1.36 - 3.82). Similar associations were also found among ER+ cases (home kit: OR 1.47, 95% CI: 0.82 - 2.63; combination: OR 2.98, 95 % CI: 1.62 - 5.49), but not ER- cases. Combination application of relaxers was associated with increased odds of tumors > 2.0 cm vs. < 1.0 cm (OR 1.82, 95 % CI: 1.23 - 2.69). Longer duration and earlier use of relaxers (before age 12 years) and combination application of permanent hair dyes and relaxers seemed to be associated with breast tumor features including higher tumor grade and larger tumor size, although the risk estimates did not reach statistical significance. The authors stated the current study did not assess the changes in hair dye and/or chemical relaxer/straightening product formulations over time might have impacted the observed risk estimates.

One meta-analysis summarized results of studies conducted from 1966 up to 2005,[24] and included 12 case-control studies, which involved a total of 5019 cases and 8486 controls, and 2 cohort studies which recruited a total of 665,993 participants with 1135 incident cases of breast cancer. The pooled RR of breast cancer was 1.06 (95% CI: 0.95 - 1.18) and nonsignificant when comparing ever-use vs. never-use of hair dyes. No significant increased risk was documented when considering intensive exposure (≥ 200 times) or restricting analyses to the use of permanent dyes only. It was noted that, giving the largely prevalent use of hair dyes in the population, frequency of use rather than simple distinction between users and nonusers, would be relevant to consider.

A meta-analysis was performed to investigate the association between hair dye use and breast cancer, including 8 case-control studies published between 1980 and 2017 with a total of 11,079 cases and 26,958 controls.[37] Of the 24 studies initially considered relevant, only 8 were considered to meet the authors' selection criteria, while 5 prospective studies which did not show any association between hair dye use and breast cancer, were not considered. The prospective studies were excluded for various reasons: HR instead of an OR/RR was used, the death rate instead of cancer incidence was recorded, no information on the number of controls was provided, no baseline category information published, and the study had a high focus on other types of cancer. Using a random effects model the pooled RR for women using hair dyes was 1.18 (95% CI: 1.03 - 1.37), which indicated an 18.8% increased risk of future development of breast cancer among hair dye users. However, the authors stated that the reliability of this systematic analysis had decreased due to the large number of excluded prospective studies. In addition, the authors indicated there was significant heterogeneity among studies involved in the meta-analysis, and no uniform adjustment for confounding factors were conducted across studies. Notably, due to the lack of accurate information regarding different exposure characteristics across multiple studies included in this meta-analysis, the authors clearly stated such meta-analysis did not provide any insights into the dose-effect relationship or the chemical constituents implicated in potential causation.

A meta-analysis was conducted to examine the relationship between hair dye use and breast cancer risk.[38] The analyzed data comprised 11 case-control studies and 3 prospective cohort studies with 210,319 subjects from the North America, Asia, Europe, and Australia. The results suggested a slightly increased breast cancer risk in hair dyes users (pooled OR = 1.07; 95% CI: 1.01 - 1.13). The ORs for specific hair products were: with permanent hair dye use OR = 1.08 (95% CI: 1.03 - 1.14), with semi-permanent hair dye use OR = 1.09 (95% CI: 0.92 - 1.28), with rinse (temporary) hair dye use OR = 1.17 (95% CI: 1.02 - 1.35), and with straightener use OR = 1.04 (95% CI: 0.96 - 1.14). No impact was identified on the overall correlation between hair dyes and breast cancer risk when subjects were stratified by race (White vs non-White: pooled OR = 1.05; 95% CI: 0.86 - 1.29), duration of use (<10 years vs. ≥10 years: pooled OR = 0.96; 95% CI: 0.85 - 1.08) or dye color (dark vs. light: pooled OR = 0.91; 95% CI: 0.62 - 1.32). Note, the Eberle et al. 2020 study[26] described above was included in such meta-analysis. The assigned weights of the Eberle et al. 2020 study wer 41.3, 25.97, 29.33, and 48.71% in the calculation of ORs for permanent hair dye use, semi-permanent hair dye use, rinse (temporary) hair dye use, and straightener use, respectively. This means that relatively high weights were given to the Eberle et al. 2020 study during the statistical calculations, which consequently had a significant influence on meta-analysis outcomes.

Ovarian Cancer

In a prospective cohort, 40,559 Sister Study participants aged 35 - 74 at enrollment (2003 - 2009) were included to assess the potential associations of permanent hair dye use and the occurrence of ovarian cancers.[39] Over an average of 10 years of follow-up, 241 women were diagnosed with ovarian cancer. The evaluation of hair dye exposure was a ++++ on the Rollison et al. (2006) scale. No positive association was observed between incident ovarian cancer with ever-use of permanent (HR 1.07, 95% CI: 0.82 - 1.39), semi-permanent (HR 1.17, 95% CI: 0.85 - 1.60) and temporary dyes (HR 0.75, 95% CI: 0.45 - 1.26). Findings were similar when ovarian cancer cases were limited to those confirmed by medical record. In addition, more frequent use of hair dye (> 4 times) or duration use (≥ 10 years) was not associated with an increased risk of ovarian cancer compared to never use. Notably, when ovarian tumors were stratified by serous versus non-serous type, ever-use of permanent hair dye was positively associated with non-serous tumors (HR 1.94, 95% CI: 1.12 - 3.37), but inversely associated with serous (HR 0.65, 95% CI: 0.43 - 0.99) tumors (heterogeneity p = 0.002). The author indicated that ovarian cancer is a rare disease (only 241 cases were diagnosed from a 10-year follow-up, large cohort of over 50,000 US women); considering that the non-serous group includes clear cell, endometrioid, and mucinous carcinomas, as well as other histologic types with different etiologies, the ovarian cancer subtype-stratified analyses were difficult to interpret.

Hematologic Cancer

A population-based case-control study of NHL was performed in Connecticut, USA.[40] There were 601 female cases (aged 21 - 84 years), and 717 age-matched (± 5 years) controls from Connecticut Tumor Registry database. The evaluation of hair dye exposure was a +++ on the Rollison et al. (2006) scale. Exposure information of hair dye use included type, cumulative applications, dye colors, and duration of use. An increased risk of NHL was observed among women who reported use of hair dyes before 1980 (OR 1.3, 95% CI: 1.0 - 1.8). In comparison, no increased risk of NHL overall and by subtype was found among women who started using hair-coloring products in 1980 or later (OR 0.9, 95% CI: 0.7 - 1.3). Specifically, the ORs were 2.1 (95% CI: 1.0 - 4.0) for women using darker permanent hair dye for ≥ 25 years and 1.7 (95% CI: 1.0 - 2.8) for women who had more than 200 applications. Further stratified analysis by subtype of NHL showed that

Follicular type (OR 1.9, 95% CI: 1.1 - 3.2), B-cell (OR 1.6, 95% CI: 1.2 - 2.3), and low-grade lymphoma (OR 1.6, 95% CI: 1.0 - 2.5) generally were associated with an increased risk with permanent hair dye uses prior to 1980.

In a population-based case-control study on NHL conducted in the USA, there were 1321 cases (aged 20 - 74 years) and 1057 age-, sex-, race-, and residency-matched controls from Iowa, Los Angeles County, metropolitan Detroit, and metropolitan Seattle.[41] Known HIV-positive cases were excluded. Detailed information on patterns of hair dye use included duration of use, annual use frequency, number of lifetime use, hair dye type, color and intense tone. The evaluation of hair dye exposure was a ++++ on the Rollison et al. (2006) scale. There were no overall association between permanent, semi-permanent and temporary hair dye use and bladder cancer risk among women or men. Risk estimates were higher for use before 1980 than for use after 1980, particularly for use of permanent, intense tone (black, dark brown, dark blonde) products (< 1980: OR = 1.6, 95% CI: 0.9 - 2.7; ≥ 1980: OR = 0.6, 95% CI: 0.4 - 1.1). In subgroup analysis, women with ≥ 100 lifetime applications had a significantly elevated OR of 1.4 (95% CI: 1.0 - 2.0). Increased risk was also observed in women who used permanent, intense color tone products for ≥ 15 years prior to 1980 (OR = 3.9, 95% CI: 1.2 - 12.5), but no consistent dose-response patterns were observed with frequency, duration, or total lifetime applications.

A hospital-based case-control study of acute myeloid leukemia (AML) was conducted in Shanghai, China.[42] The investigation consisted of 722 newly diagnosed AML cases and 1444 individually gender-age-matched patient controls at 29 hospitals in Shanghai. AML cases were further stratified to four subgroups, including AML-RCA (AML with recurrent cytogenetic abnormalities), APL (Acute promyelocytic leukemia), AML-MD (AML with multilineage dysplasia) AML-noc (AML not otherwise categorized). The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale. There was no increase in the risk of personal use of hair dyes with AML-total (OR 0.98, 95% CI: 0.80 - 1.20), or the subgroups. In comparison, the study identified a number of risk factor for AML, such as smoking, particularly among the male subjects, as well as alcohol consumption and a low level of education.

A hospital-based case-control study was conducted on 649 NHL cases in Shanghai, China.[43] The analysis included 1298 controls and the evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale. There was no increase in the risk of personal use of hair dyes with NHL-total (OR 0.93, 95% CI: 0.75 - 1.16), or any of its subtypes, such as B-Cell neoplasms (OR 0.94, 95% CI: 0.74 - 1.19), follicular lymphoma (FL) (OR 1.57, 95% CI: 0.72 - 3.46), and T/NK-cell neoplasms (OR 0.88, 95% CI: 0.48 - 1.61). For chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL), the authors reported a significantly lower risk associated with hair dye use (OR 0.37, 95% CI: 0.18 - 0.76). The author stated it appeared the use of hair dyes is not a risk factor for overall NHL, but certain subtypes could be more likely to be affected, and thus more studies focusing on specific subtypes were warranted.

Tissue samples from a population-based case-control study of NHL in males from Iowa and Minnesota were subjected to re-evaluation using FISH (fluorescence in situ hybridization) cytogenetic technique to examine both *tpwle*;18)-positive and *t*(14;18)-negative NHL subtypes and immunohistochemistry (IHC) assays to evaluate expression of the anti-apoptotic protein bcl-2.[44] There were 8 *t*(14;18)-positive, 12 *t*(14;18)-negative, 20 bcl-2 positive, and 4 bcl-2 negative NHL cases and 58 control subjects in the subpopulation tested (i.e., men having used hair dye at least once a month for at least one year, or occupational exposure to hair dyes on any job held for at least a year). Evaluation of hair dye exposure scored + on the Rollison et al. (2006) scale. Adjusting for age, state, and proxy status (i.e., whether or not next-of-kin proxies were interviewed), a statistically-significant association between ever/never use of hair dyes and *t*(14;18)-negative NHL (OR 2.90; 95% CI: 1.60 - 5.00) and bcl-2 positive NHL (OR 2.20, 95% CI: 1.40 - 3.40), but not with *t*(14;18)-positive NHL (OR 1.30, 95% CI: 0.60 - 2.60) or bcl-2 negative NHL (OR 1.40, 95% CI: 0.50 - 3.80). Similarly, smoking was associated with *t*(14;18)-negative NHL, but not clearly associated with *t*(14;18)-positive NHL, bcl-2 negative NHL, or bcl-2 positive NHL in this study.

A hospital-based case-control study of myelodysplastic syndromes (MDSs) was performed in China.[45] There were 403 diagnosed cases and 806 gender and age-matched patient controls from 27 major hospitals in Shanghai. Information on hair dye use frequency (< 2 time/year, ≥ 2 times/year) and accumulative uses (< 70 times, ≥ 70 times) was collected. The evaluation of hair dye exposure was a ++ on the Rollison et al. (2006) scale. In a univariate analysis, the OR for hair dye use (≥ 2 times per year) and all MDSs was 1.46 (95% CI: 1.03 - 2.07). In a multivariate analysis performed to adjust for potential confounding factors, the OR was not statistically significant (OR 1.31, 95% CI: 0.88 - 1.93), indicating that hair dye use (≥2 times/year) was a relative risk factor, not an independent risk factor. Associations were also examined between hair dye use (frequency and duration) with MDS subtypes refractory anemia with excess of blasts (RAEB) and refractory cytopenia with multiple dysplasia (RCMD), all results were negative. In comparison, smoking was associated with the development of MDSs in the univariate analysis and with RAEB in both the univariate and multivariate analyses.

A hospital-based case-control study was conducted to investigate the hair dye use in the etiology of leukemia and lymphoma in Egypt.[46] There were 130 cases, including 23 cases of CLL and 107 cases of NHL, and 130 age and sex-matched controls. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale. In a univariate analysis, no statistically significant association was found between these lymphoproliferative disorders and history of using hair dyes, family history of cancer, exposure to X-rays, or smoking ($\chi^2 = 0.47$, $p > 0.05$).

A population-based case-control study was conducted to evaluate whether the hair dye use influenced the risk of leukemia and NHL in Italy.[47] The analysis was restricted to women in the population studies because too few of the men reported any hair dye use. There were 161 cases (120 lymphoid and 41 myeloid) and 84 controls among the women. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale, because only duration of hair dye use < 15 years vs. ≥ 15 years was evaluated. In a multivariate analysis, the OR was 2.3 (95% CI: 1.0 - 4.9), with p = 0.036 for a trend, for NHL in women using hair dye for at least 15 years. No association was found between lymphoid malignancies and tobacco smoking or the consumption of alcoholic beverages in this study.

A hospital-based case-control study was performed in Pakistan.[48] The analysis comprised 25 adult leukemia cases with 50 gender- and marital status-matched controls, and 40 child cases with 80 age- and gender-matched controls. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale. Increased leukemia risk was observed among hair dye users. The un-adjusted OR was 4.14 (95% CI: 1.28 - 4.95) for adults who reported ever-use of hair dye and 4.60 (95% CI: 1.57 - 4.60) for children (whose mothers reported their ever-use of hair dye during interview), respectively. Other factors significantly relevant to leukemia status included exposure to chemical factory, a positive family history of leukemia, a positive trauma history, etc.

A hospital-case-control study was carried out in China to investigate the relationship between childhood leukemia and breastfeeding.[49] The subjects included 958 cases (580 boys, 378 girls) and 785 controls (449 boys, 336 girls) within the period between 2008 and 2017 at the Children's Hospital of Zhejiang University. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale. Multivariable regression analysis indicated that mothers' use of hair dye during breastfeeding was a significant risk factor for childhood leukemia (OR 13.56, 95% CI: 1.11 - 165.20). In addition, multiple other factors were identified to be associated with increased risk of childhood leukemia, such as smoking during pregnancy, a history of using birth control pills before pregnancy, abortion history, and mothers having lower education level.

A hospital-based case-control study was conducted among acute lymphocytic leukemia (ALL) cases in Iran, involving 125 cases (age younger than 15 years) and 130 controls matched with age, gender, and residence location.[50] The evaluation of hair dye exposure scored + on the Rollison et al. (2006) scale. No significant association was observed between the risk for ALL and mother's use of hair dye during pregnancy (OR 0.87, 95% CI: 0.32 - 2.37).

A meta-analysis involving 31 case-control studies and 9 cohort studies was carried out to examine the association between hair dye use and the incidence of hematopoietic cancers (including NHL, Hodgkin lymphoma, multiple myeloma, and leukemia).[24] When all hematopoietic cancers were analyzed together, the pooled RR for ever-users of hair dye was 1.15 (95% CI, 1.05 - 1.27). The increased risk is restricted to case-control studies (pooled RR 1.23, 95% CI: 1.09 - 1.39); in comparison, no risk increase was observed when all cohort studies were combined (pooled RR 1.01, 95% CI: 0.89 - 1.16). More specifically, the increase in case-control studies is restricted to the 17 case-control studies with data on men (pooled RR 1.57, 95% CI: 1.33-1.84). No cohort study with data on men was available for comparison. Additionally, the results of intensive exposure did not show any association between hair dyes exposure and hematopoietic cancers (RR 1.12, 95% CI: 0.98 - 1.28).

A meta-analysis involving 4 case-control studies was performed to examine the link between personal use of hair dye and risk of NHL.[51] The analysis included 4461 cases and 5799 controls that were enrolled in the International Lymphoma Epidemiology Consortium (InterLymph) 1988 - 2003. Increased risk of NHL (pooled OR 1.3, 95% CI: 1.1 - 1.4) was observed among women who began using hair dye before 1980, but not among women who started use in 1980 or later (pooled OR 1.1, 95% CI: 0.9 - 1.2). Further stratified analyses by NHL subtype were conducted in subjects who started using hair dyes before 1980. The results indicated increased risk for FL (OR 1.4, 95% CI: 1.1 - 1.9) and CLL/SLL (OR 1.5, 95% CI: 1.1 - 2.0) but not for other NHL subtypes. In addition, risk of NHL was not associated with hair-dye use before or after 1980 among men. The authors indicated that many oxidative hair dye products were reformulated in the early 1980s in the US to eliminate ingredients that produced tumors in animal bioassays; thus, the current analysis investigated the relation between hair dye use and NHL risk by separating persons who started using hair dyes before 1980 from those who started using them later.

A meta-analysis of 19 case-control studies of NHL subtypes was conducted, focusing on FL.[52] No associations between FL and hair dye use type, duration, or frequency were found in this study, except for a modest increase in women who used hair dyes before 1980 (OR 1.40, 95% CI: 1.10 - 1.78). In comparison, the risk of FL in women was associated with current cigarette smoking, trending higher with increasing duration of smoking.

A meta-analysis of 19 case-control studies of NHL subtypes was performed (4,667 cases and 22,639 controls), focusing on diffuse large B-cell lymphoma (DLBCL).[53] There were no overall and sex- or age-specific associations between DLBCL and hair dye use, based on the basic adjusted model results of this study. The OR for mediastinal DLBCL was 4.97 (95% CI: 1.63 - 15.15) for use of hair dyes for at least 20 years, compared with never used hair dyes. When analysis stratified by ever hair dye us before or after 1980, there was no associated risk with DLBCL was identified, the OR was 2.75 (95% CI: 0.91 - 8.29) and 0.56 (95% CI: 0.22 - 1.45) for ever hair dye use <1980 for hair dye use only ≥1980, respectively. Using hair dyes for at least 20 years was not associated with DLBCL at other anatomical sites, including the central nervous system (CNS),

testis, gastrointestinal tract, and skin. Use of hair dyes for less than 20 years was not associated with DLBCL at any site. In comparison, smoking was associated with CNS, testicular and cutaneous DLBCLs in this study. The authors indicated the results were not adjusted for multiple comparisons.

A meta-analysis of 16 case-control and 4 cohort studies of leukemias (stratified by subtype of AML, ALL, chronic myeloid leukemia (CML), CLL, and SLL) has been performed in 2017.[54] Ever-use of hair dye was associated with a non-statistically significant increased risk of leukemia (meta-RR 1.09, 95% CI: 0.97 - 1.22). Specifically, with permanent hair dye use RR = 1.19 (95% CI: 1.07 - 1.33), with dark hair dye use RR = 1.29 (95% CI: 1.11 - 1.50), with hair dye use among males RR = 1.42 (95% CI: 1.01 - 2.00), with hair dye use pre-1980 RR = 1.49 (95% CI: 1.21 - 1.83), and with hair dye use for longer than 15 years RR = 1.35 (95% CI: 1.13 - 1.62). When adjustment of smoking was conducted, ever-use of hair dye was not associated with leukemia, meta-RR = 0.99 (95% CI: 0.76 - 1.29). Overall, results indicated that ever-use of hair dye was not a significant risk factor for leukemia.

A meta-analysis aimed at analyzing the association between hair dye use and the pathogenesis of NHL was conducted in 2019, including 13 case-control studies and 3 cohort studies (with 720,019 participants) published between 1988 to 2015.[55] The 13 case-control studies included a total of 10,399 NHL cases and 20,013 controls and the 3 cohort studies reported 928 NHL cases. The OR value of the case-control studies or cohort studies was 1.13 (95% CI: 0.86 - 1.84) or 1.16 (95% CI: 0.91 - 1.69), respectively. When all studies were combined, the OR value was 1.14 (95% CI: 1.01 - 1.29), indicating that the risk of NHL in hair dye users was 14%; however, heterogeneity index I^2 was 79.7%, suggesting that there was significant heterogeneity among these diverse studies. In addition, the duration of hair colorant use recorded in these studies was divided into 3 groups: < 10 years (OR 1.19, 95% CI: 0.90 - 1.88), 10 - 20 years (OR 1.20; 95% CI: 1.02 - 1.95), and > 20 years (OR 1.34, 95% CI: 1.04 - 1.92). The results suggested that people who used hair dyes for more than 20 years had increased risk of NHL.

In a meta-analysis involving 5 case-control studies, the association between history of hair dye use and risk of FL was assessed within a total of 4687 cases and 30,137 controls.[56] The period of data collection spanned 1976 - 2009. Hair dye use before 1980 was positively associated with FL risk (RR 1.66; 95% CI: 1.22 - 2.25) and no evidence of effect was observed after 1980.

A meta-analysis involving 28 case-control studies (12,313 cases and 27,955 controls) was performed to investigate the association between hair dye use and the incidence of hematopoietic cancers.[57] In the 17 studies that assessed general use of any type of hair dyes and cancer rates, the pooled OR of hematopoietic cancers in women was 1.10 (95% CI: 1.01 - 1.20, I^2 = 58.2%). There were 11 studies investigating hair dye manufactured before and after 1980 as a risk factor for cancer; the pooled OR was 1.31 (95% CI: 1.08 - 1.59, I^2 = 59.5%) for using hair dye made before 1980, while the use of hair dye made after 1980 was not associated with cancer incidence (OR = 0.99; 95% CI: 0.89 - 1.10, I^2 = 1.9%). In the 13 studies examining the use of light and dark hair dye, the use of dark hair dye was associated with increased cancer rates (OR = 1.09; 95% CI: 0.95 - 1.25, I^2 = 47.8%).

Bladder Cancer

A hospital-based case-control study was performed in Spain, with 152 women cases and 166 age-, gender-, and hospital-matched controls.[58] Detailed information on patterns of hair dye use included year first used, as well as type, duration and frequency of uses. The hair dye exposure assessment was a ++++ on the Rollison et al. (2006) scale. No increased risk was associated with use of any hair dye (OR 0.8, 95% CI: 0.5 - 1.4) or of permanent hair dyes (OR 0.8, 95% CI: 0.5 - 1.5). No significant increase in risk was observed for use hair dyes at least 10 times (OR 1.3, 95% CI: 0.8 - 2.2). In addition, there was no trend in risk was seen with increasing exposure for duration of use, average use, or cumulative use. All models were adjusted for age, region, and smoking status.

To investigate risk factors for bladder cancer in Iran, a population-based case-control dataset with 692 cases and 692 gender- and age-matched controls was analyzed.[59] Cases were identified using the Iranian cancer registry. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale. The OR for hair dye use and bladder cancer was 1.81 (95% CI: 1.08 - 3.06). After adjustment for cigarette smoking, the OR was 1.99 (95% CI: 1.02 - 3.82). When women and men were analyzed separately, no significant association between hair dye use and bladder cancer was found.

A population-based case-control study was conducted in Maine, Vermont, and New Hampshire.[60] The subjects were 1193 cases of urinary bladder cancer diagnosed from 2001 to 2004 (911 male and 282 female), and 1418 controls (1,039 male and 379 female). The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. The hair dye models were adjusted for age, race, sex, and smoking status. No association was found between ever/never use of hair dyes and bladder cancer – the OR and associated 95% CI: for women was 0.70 (95% CI: 0.50 - 1.00), and for men 0.70 (95% CI: 0.40 - 1.00). Because of the excellent exposure assessment, the authors were able to examine subsets of the population studied. Women who used red hair colors, for example, exhibited an OR of 0.40 (95% CI: 0.20 - 0.80), suggesting a significantly lower risk of bladder cancer associated with the use of such hair dyes. A similar lower risk of bladder cancer was reported for women who used hair dyes for a duration between 10 and 19 years (OR 0.5, 95% CI: 0.27 - 0.79). As the data were further analyzed, the authors considered women with and without college degrees. Women without college degrees who

used permanent hair dyes exclusively, for example, had a significantly lower risk of bladder cancer (OR 0.50, 95% CI: 0.40 - 0.70). Exclusive use of permanent hair dyes by women with college degrees was associated with a significantly higher risk of bladder cancer (OR 4.90, 95% CI: 1.70 - 14.60). No statistically significant interactions with hair-dye use were found when the data were stratified by state of residence, hair-dye product type, smoking, age at diagnosis/interview, or disease aggressiveness in the female subjects.

In a population-based case-control study conducted in the Netherlands, the subjects were 1385 cases (n = 246 women) and 4754 (n = 2587 women) controls, recruited in the Nijmegen Bladder Cancer (NBC) Study; all of the subjects for which the analyses were performed were women (less than 5% of the men selected for the study reported ever using hair dyes).[61] The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. All analyses were adjusted for age and smoking status, duration, and intensity. Additional adjustment for education level and other variables considered were not included in the final model because they did not change the standardized regression coefficient (β) by more than 10%. No association was found between bladder cancer and ever-use of permanent hair dyes (OR 0.87, 95% CI: 0.65 - 1.18) or temporary hair dyes (OR 0.77, 95% CI: 0.58 - 1.02). In addition, no association was observed when hair dye use was defined by type, duration or frequency of use, dye color, or extent of use or when the patients were stratified by aggressive and non-aggressive bladder cancers.

In a meta-analysis involving 15 case-control and 2 cohort studies, the abstracted information included the variables adjusted and/or used to match control subjects with cases.[62] For example, 12 of the studies clearly adjusted for smoking; adjustment for smoking was not clear in 1 study. The pooled RR of bladder cancer incidence/mortality was 0.93 (95% CI: 0.83 - 1.05) for personal use of any type of hair dye, compared with no use, and comparable results were obtained when the subjects were stratified by sex. The RR for personal use of permanent hair dyes from 7 of the studies was 0.92 (95% CI: 0.77 - 1.09). Similarly, no association was found between bladder cancer and the duration or lifetime frequency of use of any type of hair dye or use of permanent hair dyes, compared with never used hair dyes. The RR for the use of dark-color hair dyes was 1.29 (95% CI: 0.98 - 1.71).

Brain Cancer

A population-based case-control study was conducted in the west coast of the USA (Los Angeles, San Francisco, and Seattle), with 540 childhood brain tumors (CBT) cases (aged < 20 years) and 801 birth- and sex-matched controls.[63] Interviewed mothers of the subjects reported their hair dye use (permanent, semi-permanent, temporary) before and during pregnancy. The hair dye exposure assessment was +++ on the Rollison et al. (2006) scale. Overall, exclusive use of permanent dye, semi-permanent, temporary dye or hair darkeners before or during pregnancy was not associated with risk for CBT (OR 0.96, 95% CI: 0.69 - 1.3). Risks for the three major subtypes of CBT, astrocytic tumors (OR 1.00, 95% CI: 0.69 - 1.5), primitive neuroectodermal tumors (PNET) (OR 0.97, 95% CI: 0.51 - 1.9) and other gliomas (OR 0.76, 95% CI: 0.40 - 1.4), were also not associated with the use of hair dyes during pregnancy.

A meta-analysis including 4 case-control and 2 cohort studies were conducted to investigate the hair dye use and the incidence of gliomas.[64] Matching or adjustment for age and sex was performed in all 6 studies included in this meta-analysis, and for smoking in 2 of the 6 studies. The most adjusted risk estimates were included, and the raw data were used when adjusted estimates were not available. Summary RRs for ever-use of any hair dyes were 1.13 (95% CI: 0.89 - 1.45) for all studies, 1.29 (95% CI: 0.94 - 1.78) for case-control studies, and 0.90 (95% CI: 0.78 - 1.05) for cohort studies. Similar results were obtained when the subjects were stratified by geographic regions and sex. No significant associations were found among the studies that evaluated permanent hair dye use and duration of any hair dye use.

Prostate Cancer

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study cohort, 50 - 69 year-old male smokers (n = 28,795) were recruited from 1985 to 1988 in southwestern Finland.[65] During a 28-year period of observation, 2703 incidences of prostate cancer cases were diagnosed. At the time of baseline interview, 75 men reported hair dye use, and 13 of them were diagnosed with prostate cancer thereafter. The evaluation of hair dye exposure was a + on the Rollison et al. (2006) scale. After adjustments for age, number of cigarettes smoked daily, years of smoking, and family history of prostate cancer, men who used hair dyes were associated with higher prostate cancer risk (HR 1.77, 95% CI:1.03 - 3.05), compared with those who did not use hair dyes. However, as the authors indicated, misclassification of hair dye exposure may have occurred because it was only assessed during study enrollment; consequently, hair dye use could have changed over time (e.g., baseline users might decide to stop hair coloration but not report such a change); in addition, a small number of exposed cases might result in low statistical power.

A hospital-based case-control study was conducted among prostate cancer cases in Taiwan, involving 296 cases with newly diagnosed prostate cancer and 296 age-, ethnicity-, and hospital-matched controls. Information on hair dye use was obtained through a standardized questionnaire.[66] The evaluation of hair dye exposure was ++ on the Rollison et al. (2006) scale. The prevalence of hair dye use was higher in the cases than the controls (95/296 = 32.1% vs. 64/296 = 21.6%, $p < 0.05$), and the hair dye users had increased odds of prostate cancer when compared with the non-users (adjusted OR 2.15, 95% CI: 1.32 - 3.57). The significant risks were more prominent in users aged < 60 years (OR 2.64, 95% CI:1.16 - 6.36),

who had used hair dyes for > 10 years (OR 2.54, 95% CI:1.23 - 5.41), > 6 times per year (OR 2.65, 95% CI:1.26 - 5.78), and started using hair dyes before 1980 (OR 2.16, 95% CI:1.28 - 3.68). The study found personal hair dye use increased risk of prostate cancer with a dose-response effect (p trend < 0.01). Meanwhile, to determine the rate of prostate cancer survival, another 608 incident prostate cancer cases were investigated. In the cases-only study, 26.4% (161/608) reported having used hair dyes. The mean and median follow-up times were 25.7 and 22.2 months, respectively (range from 0.1 - 84.4 months). The use of hair dye was not correlated with the clinical stage of prostate cancer (categorized by localized, locally advanced, and bone metastasis). In addition, the use of hair dye did not affect cumulative incidence estimates of prostate cancer-specific deaths (p = 0.753).

This above study was the first to show a positive association between personal hair dye use and risk of prostate cancer, revealing a dose-response relationship assessed by duration and frequency; however, cumulative exposure dose, a critical indicator to estimate a dose-response effect, was not assessed.[67] Besides, the external validity of this study has been argued. One meta-analysis targeted on occupational exposure of hairdressers observed no increased risk of prostate cancer (pooled RR 1.02, 95% CI: 0.89 - 1.18).[68] It should be noted recall bias and lack of detail information of the exposure factors can be a particular concern in case-control study design. While the finding in the study described above are limited and do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted.

Pediatric Germ Cell Tumors

A hospital-based case-control study was performed among 42 pediatric germ cell tumors (GCT) cases and 42 sex- and age-matched controls.[69] Subjects were recruited from Xinhua Hospital in Shanghai, China. Information on subject mothers' use of hair dye during pregnancy was collected by online questionnaire. The evaluation of hair dye exposure was ++ on the Rollison et al (2006) scale. All participants with a history of hair dye usage during pregnancy had significantly elevated serum perfluorohexane sulfonate (PFHxS) levels compared with those without in the GCT [2.38 (1.72–3.29) ng/ml vs. 1.37 (0.63–1.95) ng/ml, p = 0.010] or control group [0.49 (0.34–0.67) ng/ml vs. 0.32 (0.19–0.46) ng/ml, p = 0.020]. Logistic regression analysis further identified PFHxS levels were statistically significantly associated with GCTs. The OR for a 1 ng/l increase of PFHxS in serum was 19.47 (95% CI: 4.20 - 90.26). The authors concluded serum PFHxS levels were independently associated with GCT occurrence.

Testicular Cancer

A population-based case-control study was carried out among 527 mothers of testicular germ cell tumors (TGCT) cases and 562 mothers of controls.[70] The subjects (men aged 18 - 45 years) were enrolled in US Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) study between 2002 - 2005, and had at least one serum sample stored in the US Department of Defense Serum Repository. The hair dye exposure assessment was a + on the Rollison et al. (2006) scale. TGCT, accounting for approximately 98% of testicular cancers, are the most commonly occurring cancer among men aged 15 - 44 in the US though they are rare tumors in the general population.[71] Maternal use of hair dye (OR 0.80, 95% CI: 0.54 - 1.18), hairspray (OR 1.17, 95% CI: 0.89 - 1.55), or permanent wave (OR 1.18, 95% CI: 0.86 - 1.62) was not associated with TGCT risk in sons.

Uterine Cancer

In a national prospective cohort study (the Sister study described above), associations were investigated between hair dye use and incident uterine cancer among 33,947 participants aged 35 - 74 years who had a uterus at enrollment (2003 - 2009).[72] At baseline, participants reported hair dye use (permanent, semipermanent, and temporary hair dyes) in the previous 12 months, with response opinions of color of dyes (dark, light), as well as exposure duration and frequency (< 5 years, 5 - 9 years, ≥ 10 years). The evaluation of hair dye exposure was a ++++ on the Rollison et al. (2006) scale. Over a mean follow-up of 10.9 years, 378 uterine cancer cases were identified, reported as a diagnosis of endometrial cancer, uterine sarcoma, or other types of cancer in the uterus after enrollment. Use of any type of hair dye was not associated with an increased rate of uterine cancer. For example, the HR of permanent hair dye ever-use was 0.90 (95% CI: 0.74 - 1.11, n = 185), of use frequency > 4 times in the past 12 months prior to baseline was 0.69 (95% CI: 0.42-1.14, n = 121), of use duration ≥ 10 years was 0.69 (95% CI: 0.42 - 1.14, n = 112). In comparison, use of straightening products was associated with higher incident uterine cancer rates (HR 1.80, 95% CI: 1.12 - 2.88; n = 38).

Genetic Polymorphism

N*AT1, NAT2, GSTM1, GSTT1, CYP1A2 and Arg72Pro Genotype/Phenotype*

Altered genotype and phenotype of liver enzymes may activate or inactivate potential carcinogens.[60] NAT1 and NAT2 genes encode arylamine N-acetyltransferases that can deactivate (or, less commonly, potentially activate) arylamine and hydrazine chemicals. Polymorphisms in these genes determine, in part, the liver-function phenotypes. Human populations segregate into rapid, intermediate, and slow acetylator phenotypes. N-Acetylation is a major route of biotransformation of aromatic amine compounds, including those found in hair dyes. The GSTM1 gene encodes a cytoplasmic glutathione S-transferase that belongs to the μ class, which functions in the detoxification of electrophilic compounds (including

carcinogens, therapeutic drugs, environmental toxicants, and products of oxidative stress) through conjugation with glutathione. The GSTT1 gene encodes the glutathione S-transferase that belongs to the θ class, which catalyzes the conjugation of reduced glutathione to a variety of electrophilic and hydrophobic compounds. Genetic polymorphisms in GSTM1, GSTT1, and CYP1A2 also may affect the metabolism of the constituents of hair dyes.

In the population-based case-control study described above,[60] the association between hair dye use and effect modification by NAT1, NAT2, GSTM1, and GSTT1 genotypes was further evaluated among patients with bladder cancer. The hair dye models were adjusted for age, race, sex, and smoking status. The hair dye exposure assessment was ++++ on the Rollison et al. (2006) scale. An increased risk of bladder cancer was reported primarily among exclusive users of permanent dyes who had NAT2 slow-acetylation phenotypes (OR 7.30, 95% CI: 1.60 -32.60), compared to never users of dye with NAT2 rapid/intermediate-acetylation phenotypes. This increase was observed in females with a college degree, but the difference was not statistically significant. The authors concluded that NAT1, GSTM1, and GSTT1 genotypes did not appear to be important modifiers of the association between ever, permanent, or exclusive permanent hair dye use and bladder cancer.

In another population-based case-control study including 159 women cases and 164 sex-, race-, age-, and residency-matched controls, modifying effects of seven genotypes/phenotypes (GSTM1, GSTT1, GSTP1, NAT1, NAT2, CYP1A2) on the permanent hair dye-bladder cancer association were evaluated.[73] The evaluation of hair dye exposure was a +++ on the Rollison et al. (2006) scale. Individuals with the NAT2 slow-acetylator phenotype who exclusively used permanent hair dyes had an increased risk of bladder cancer (OR 2.90, 95% CI: 1.20 - 7.50) after adjustment for cigarette smoking, compared to individuals with the NAT2 rapid-acetylator phenotypes (OR 1.30, 95% CI: 0.60 - 2.80). The NAT*10 allele contains an altered polyadenylation signal that has been associated with elevated DNA adduct levels and greater risk of bladder cancer in other studies. Individuals with a NAT1*10 genotype who were non-smokers and used permanent hair dyes exclusively had an OR of 1.00 (95% CI: 0.20 - 4.30), and those with a non-NAT1*10 genotype had an OR of 6.80 (95% CI: 1.70 - 27.40) in this study.

A hospital-based case-control study that evaluated the association of hair dye use with bladder cancer among females also examined the effect of hair-dye use among genetic subgroups.[58] The hair dye exposure assessment was a ++++ on the Rollison et al. (2006) scale. ORs were estimated after adjustment for age, region, and smoking. No statistically significant differences in bladder cancer incidence were noted as a function of any of the genotypes examined, including those with slow- or intermediate/rapid-NAT2 acetylator phenotypes. For NAT2 slow-acetylator phenotypes, the OR was 0.60 (95% CI: 0.30 - 1.40), and for NAT2 rapid/intermediate phenotypes, the OR was 0.90 (95% CI: 0.30 -2.60). Individuals with a NAT1*10 genotype had an OR of 2.90 (95% CI: 0.70 - 11.60), and those with non-NAT1*10 had an OR of 0.60 (95% CI: 0.20 - 1.60). These findings were directionally opposite to those of Gago-Dominguez et al. (2003).[73]

A population-based case-control study was conducted to explore the relationship between hair dye use and the incidence of NHL.[41] The evaluation of hair dye exposure was ++++ on the Rollison et al. (2006) scale. Subjects were identified among residents of 4 Surveillance Epidemiology and End Results (SEER) registries (Iowa, Los Angeles County, and metropolitan Detroit and Seattle). There were 101 cases and 98 control subjects reporting no use of hair coloring products and 509 cases and 413 control subjects among the women reporting use of such products in the population studied. There were 317 cases and 269 control subjects reporting the use of hair dyes before 1980 and 192 cases and 148 controls reporting hair dye use in 1980 or thereafter. The risk estimates were adjusted for age, sex, race and SEER area; education, smoking status, history of farming, having a first-degree relative with a history of NHL or lymphoproliferative malignancy were excluded from the final models because these factors did not materially alter (> 10%) the parameter estimates. Among the women who started using permanent, intense-tone hair dyes before 1980, those with the NAT2 slow-acetylator phenotype (23 cases/14 controls) or who had no copies of the NAT1*10 allele (26 cases/16 controls) did not have an increased risk of NHL (OR was 1.50 (95% CI: 0.60 - 3.60) and 1.50 (95% CI: 0.70 - 3.30), respectively). Likewise, women in this subpopulation with 1 or 2 copies of the NAT1*10 allele (22 cases/10 controls) did not have an increased NHL risk (OR 2.50, 95% CI: 0.90 - 7.60). However, women with the NAT2 rapid/intermediate-acetylator phenotype who started using such dyes before 1980 (25 cases/11 controls) did exhibit a potentially increased NHL risk (OR 3.30, 95% CI: 1.30 - 8.60). There was no evidence of increased risk among women who began using hair dyes after 1980.

One study re-evaluated data from a case-control study of NHL (overall and by its subtypes) in Connecticut to consider NAT1 and NAT2 genotype/phenotype and 17 other single nucleotide polymorphisms (SNPs).[74] The subjects, including 461 cases and 535 control subjects, were identified from Connecticut Tumor Registry database (same study population as examined in Zhang et al. 2004 study.[40] Potentially confounding variables included in the final model were age and race. Adjustment for cigarette smoking, alcohol consumption, and farming history were not included in the final models because these factors did not materially alter the parameter estimates. The evaluation of hair dye exposure was +++ on the Rollison et al. (2006) scale. The associations between hair dye use and risk of NHL and it subtypes among women who carried 1 or 2 NAT1*10 alleles did not differ significantly from those for women who did not carry any NAT1*10 allele. Among women with rapid/intermediate NAT2 phenotypes, those who had used hair dye before 1980 had slightly higher risks for NHL overall (OR 1.60, 95% CI: 1.00 - 2.70), FL (OR 2.80, 95% CI: 1.10 - 7.20), and CLL/SLL (OR 3.2, 95% CI: 1.00 - 10.20), whereas these increases were not observed among women who were slow acetylators. In women who carried the CYP2C9

allele (TT or CT genotypes) and started to use hair dyes before 1980, there was an increased risk of NHL in general (OR 2.9, 95% CI: 1.40 - 6.10), and the OR reached 6.3 (95% CI: 1.60 - 24.70) in FL subtype. In contrast, no significantly increased risk was observed for starting hair dye use before 1980 (relative to never use) among women who were homozygous wild-type for the CYP2C9, CYP2E1, or GSTM3 polymorphisms, women carrying 1 or 2 copies of the variant GSTP1 allele, or women who were slow NAT2 acetylators.

In a cohort of 327 women (age > 17 years) diagnosed with benign breast disease in Brazil, the SNP Arg72Pro frequency of TP53 gene was investigated.[75] The evaluation of hair dye exposure was + on the Rollison et al. (2006) scale. However, it should note subjects were exposed to a mixture of hair products (hair dyes, straighteners or relaxers exposure combined). Arg/Pro genotype was the most frequent in the studied population (44.6%), followed by Arg/Arg genotype (39.1%), and Pro/Pro genotype (16.3%). Exposure to hair products (hair dyes, straighteners or relaxers exposure combined) were statistically more frequent among women with Arg/Arg genotype (96.1%) when compared with women with another genotypes ($p = 0.039$). Analysis with Pro/Pro genotype as the reference showed that a strong interaction was observed between exposure to hair products and Arg/Arg genotype (OR 3.26, 95% CI: 1.21 - 8.82).

DNA Repair-Enzyme Genes

One study investigated the interaction between polymorphisms in DNA repair genes and hair dye use with NHL in a population-based case-control study in Connecticut.[76] The study population from which the subjects were drawn was the same as that of Zhang et al. 2004 study,[40] including 461 cases and 535 control subjects identified from Connecticut Tumor Registry database. The subjects included 518 NHL cases and 597 age-matched controls. All subjects were genotyped for 24 SNPs in 16 DNA repair-enzyme gene polymorphisms. The hair dye exposure assessment was +++ on the Rollison et al. (2006) scale. All of the models were adjusted for age, race, and smoking status. Ten genotypes in combination with hair dye use before 1980 were associated with FL risk. The ORs ranged from 1.93 (95% CI: 1.00 - 3.72; 15 cases and 70 control subjects with EECC1rs3212961 CC) to 3.28 (95% CI: 1.27 - 8.50; 7 cases and 110 control subjects with BRCA2rs144848 AC+CC). In addition, there was a statistically-significant interaction between hair dye use before 1980 and NHL in women with one of these 10 SNPs (OR 1.88, 95% CI: 1.26 - 2.80; 146 cases and 100 control subjects with WRNrs1346044 TT). No association was identified between NHL, FL, or DLBCL in women who began using hair dyes after 1980.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer.

TABLES

Table 1. Cohort studies considered by the Panel.				
Author	**Study type/Methodology**	**Results**	**Adjustment/Note**	**Study scale***
Multiple Cancer Type Measurement				
Zhang et al. 2020[21]	Large prospective cohort study started in 1976 and followed up to 2012, with 121,700 US female nurses enrolled (30-55 years old) in the national Nurses' Health Study. Data collection on permanent hair dyes use were detailed in duration of use (no-use, <5 years, 5-9 years, ≥ 10 years), frequency of use (no-use, every ≥5 weeks, every 1-4 weeks), cumulative dose (no-use, 1-99 times, 100-199 times, ≥ 200 times), age at first use (no-use, < 30 years, ≥ 30 years), and time since first use (no-use, < 30 years, ≥ 30 years).	During 36 years of follow-up, a total of 20,805 solid cancers and 4860 cancer related deaths were documented. Overall, no association was identified between ever-users of permanent hair dyes and risk of solid cancers under investigation (HR 0.98, 95% CI: 0.9 -1.01). Ever-users did not have an increased risk of cancer related deaths (HR 0.96, 95% CI: 0.91-1.02). No significant increases in risk of the following cancer types (for any hair color use): Cutaneous squamous cell carcinoma (HR 1.00, 95% CI: 0.93 - 1.09; n = 2792) Bladder cancer (HR 1.05, 95% CI: 0.90-1.24; n = 596) Melanoma (HR 1.01, 95% CI: 0.89-1.14; n = 1198) Breast cancer (HR 1.02, 95% CI: 0.98-1.07; n = 9252) Brain cancer (HR 0.72, 95% CI: 0.56-0.93; n = 277) Colorectal cancer (HR 1.05, 95% CI: 0.97-1.14; n = 2394) Kidney cancer (HR 1.03, 95% CI: 0.85-1.23; n = 477) Lung cancer (HR 0.9, 95% CI: 0.87-1.01; n = 2623) Ovarian cancer (HR 1.09, 95% CI: 0.97-1.22; n = 1215) All hematopoietic cancer (HR 1.00, 95% CI: 0.91-1.10; n = 1807) All non-Hodgkin lymphomas (HR 0.94, 95% CI: 0.84-1.05; n = 1277) Basal cell carcinoma risk was slightly increased for ever-users (HR 1.05, 95% CI: 1.02-1.08; n = 22,560), especially among women with naturally light hair color (HR 1.06, 95% CI: 1.02-1.11; n = 11,334), but not among women with naturally dark hair color (HR 1.01, 95% CI: 0.96-1.06; n = 7737). When basal cell carcinoma and cutaneous squamous cell carcinoma were excluded from analysis, the overall HR for all cancers under investigation was 1.00 (95% CI: 0.96-1.05). An increased risk of Hodgkin lymphoma was observed only for women with naturally dark hair (HR 3.89, 95% CI: 1.61-9.40; n = 24).	All models adjusted for age, race, natural hair color, BMI, smoking, and alcohol; additional adjustment might apply for specific cancer type. Self-administered questionnaires indicated hair dye ever-users were more likely to be smokers and consumed more alcohol than those reporting no permanent hair dye use. Subgroup analyses were further performed according to race/ethnicity, cumulative doses, natural hair color, as well as subtypes of breast cancer (stratified by hormone receptor status: estrogen receptor and progesterone receptor). The authors claimed that the generalizability of current findings is limited to white US women and might not extend to other populations. Additionally, cohort was not randomly sampled from US women, but enrolled only nurses and more than 96% of the women had European ancestry. The authors stated the exposure assessments ceased relatively early during cohort follow-up, thus exposure domains might be underestimated.	+++
Mendelsohn et al. 2009[22]	Prospective cohort study conducted in China, with a total of 70,366 women (aged 40-70 years) recruited in Shanghai Women's Health Study between 1996-2000 and followed up to 2005. Exposure was detailed in duration of hair dye use (no-use, 1-2 years, 3-4 years, 5-9 years, ≥10 years).	Generally, no evidence of an association was identified between personal use of hair dye and cancer risk. Compared with no use, ever-users had an overall cancer risk of 0.89 (95% CI: 0.82-0.97; n = 2437). No significant association was observed for the following cancers: Breast cancer (RR 0.93, 95% CI: 0.78-1.09; n = 592) Bladder cancer (RR 1.14, 95% CI: 0.49-1.84; n = 32) Brain cancer (RR 0.96, 95% CI: 0.56-2.35; n = 39) Colorectal cancer (RR 1.04, 95% CI: 0.84-1.28; n = 390) Kidney cancer (RR 1.11, 95% CI: 0.64-1.92, n = 54) Lung cancer (RR 0.81, 95% CI: 0.62-1.09; n = 249) Ovarian cancer (RR 0.89, 95% CI: 0.59-1.35; n = 100) Pancreatic cancer (RR 0.88, 95% CI: 0.55-1.41; n = 79) Stomach (RR 0.90, 95% CI: 0.66-1.21; n = 188) Thyroid cancer (RR 0.42, 95% CI: 0.25-0.69; n = 88)	Cox proportional hazards models adjusted for age, education and smoking duration in pack/years. About 9% of all hair dye users in the cohort (2689 individuals) reported ≥10 years of hair dye use. Hair dye users had a median age of 51 years; hair dye use ranged from 1-52 years, with a median of 3 years and a mean of 3.8 years of use. Women who had not used hair dye in the three years prior to interview were classified as nonusers. The study is limited by small numbers for certain cancer types.	+

Table 1. Cohort studies considered by the Panel.				
Author	**Study type/Methodology**	**Results**	**Adjustment/Note**	**Study scale***
		Uterine cancer (RR 1.10, 95% CI: 0.77-1.58; n = 125) Hematopoietic cancers (RR 0.89, 95% CI: 0.59-1.35; n = 99), or their subtypes, including NHL (RR 1.09, 95% CI: 0.61-1.92; n = 51), multiple myeloma (RR:0.84, 95% CI: 0.31-2.27; n = 18), and leukemia (RR 0.68, 95% CI: 0.31-1.51; n = 29)		
Thun et al. 1994[23]	Prospective cohort study conducted in the USA, with a total of 573,369 women (age ≥30 years, median age 56 years) enrolled from CPS-II study in 1982, and followed up to 1989. Data were detailed in duration of hair dye use (no-use, 1-9 years, 10-19 years, ≥ 20 years), and dye colors (blond, red/auburn, brown, black, other dye).	Permanent hair dyes showed decreased risk of all fatal cancers combined (RR = 0.93, 95% CI = 0.89-0.98), and of urinary system cancers (RR = 0.65, 95% CI = 0.49-0.87), No increase in risk of any type of the following cancers: Breast cancer (RR 0.95, 95% CI: 0.83-1.08) Bladder cancer (RR 0.56, 95% CI: 0.32-0.99) Brain and other nervous system (RR 0.85, 95% CI: 0.67-1.09) Digestive system (RR 0.94, 95% CI: 0.85-1.03) Respiratory system (RR 1.00, 95% CI: 0.91-1.11) Oral cavity and pharynx (RR 0.61, 95% CI: 0.32-1.14) All hematopoietic cancer (RR = 0.94, 95% CI = 0.80-1.10) Women who had used black hair dyes for 20 years (0.6% of women hair dyers) or more had increased risk of fatal NHL (RR = 4.37, 95% CI = 1.3-15.2; n = 3) and multiple myeloma (RR = 4.39, 95% CI = 1.1-18.3, n = 2). However, it should note the number of cases were very small, the statistical power of these sub-analyses was limited.	Models adjusted for age, race, and smoking. The authors indicated the limitations of the study: it depended on a single, self-administered questionnaire; it relied on mortality rather than incidence to define disease; with no information on hair dye type.	++
		Breast Cancer		
Eberle et al. 2020[26]	Prospective cohort study of breast cancer in the United States and Puerto Rico. Subjects from Sister Study included 46,709 women aged 35-74 enrolling from 2003 to 2009, who had no history of breast cancer but had 1 or more sisters with breast cancer. Participants reported their personal hair dye use in the 12 months before enrollment. Detailed hair dye use patterns included dye type (permanent, semi-permanent, temporary), color (dark, light, or both), duration (no-use, <5 years, 5-9 years, ≥10 years), and frequency (no-use, 1-2 times per year, every 3-4 months, every 5-8 weeks, 1 time/month, >1 time/month).	During a mean of 8.3 years follow-up, 2794 breast cancers were identified. 55% of participants reported using permanent dye at enrollment. For permanent dye use, HR was 1.45 (95% CI: 1.10 - 1.90, n = 102) in black women, and 1.07 (95% CI: 0.99 - 1.16, n = 1338) in white women (heterogeneity p = 0.04). A higher breast cancer risk was observed in light dye use (HR 1.12; 95% CI:1.02-1.23, n = 713) compared to dark dye use (HR 1.08; 95% CI: 0.98-1.19, n = 683). Non-professional application of semi-permanent dye to others was associated with breast cancer risk (HR 1.28, 95% CI: 1.05-1.56; n = 105), while association was not found for non-professional application of permanent dye to others (HR 0.99, 95% CI: 0.85-1.15; n = 188) However, no significant association is seen between permanent hair dye use and breast cancer risk in both white and black women when analysis was stratified by durations of use: HR = 1.08 (95% CI: 0.77-1.52, n = 53) for duration of use < 5 years in black women HR = 0.97 (95% CI: 0.70-1.34, n = 59) for duration of use ≥ 5 years in black women HR = 1.08 (95% CI: 0.77-1.52, n = 376) for duration of use < 5 years in white women HR = 1.06 (95% CI: 0.97-1.16, n = 1177) for duration of use ≥ 5 years in white women There was no association between semi-permanent dye/temporary dye use and breast cancer risk.	Models adjusted for age, race, education, oral contraceptive use, parity, age at first birth, smoking status, BMI, age at menarche, and menopausal status. Women were recruited to the study because they had a sister with breast cancer, meaning all subjects in the current study had a significant risk factor of breast cancer, so the conclusions cannot be extended to the wider population;	++++
White et al. 2021[29]	Prospective cohort study of breast cancer in the United States and Puerto Rico. Sister Study participants (ages 35-74 years) who had completed enrollment questionnaires (2003-2009) on use of hair dyes, straighteners/relaxers, and permanent waves (perms) at ages 10-13 years (n = 47,522) were followed up to 2018.	Over an average of 10 years of follow-up, 3380 breast cases were diagnosed. Hair dyes use were not associated with breast cancer risk overall or by menopausal status: permanent (HR 0.97, 95% CI: 0.78-1.20) or semi-permanent hair dye use (HR 0.87, 95% CI: 0.68-1.12) during adolescence was uncommon (< 3%) and not associated with breast cancer. A higher risk for breast cancer was observed in black women (HR 1.77, 95% CI: 1.01-3.11; n = 13), but not among white women (HR 0.93; 95% CI: 0.74-1.18, n = 70).	Models adjusted for race, education, and household income. Most black women who reported using permanent hair dye during adolescence reported also using permanent hair dye in the 12 months prior to study baseline (n = 10 of 13 exposed cases), thus the authors stated they could not reliably estimate	++

Table 1. Cohort studies considered by the Panel.				
Author	**Study type/Methodology**	**Results**	**Adjustment/Note**	**Study scale***
	Information on hair dye type (permanent, semi-permanent, temporary) and frequency of use (sometimes or frequently) were collected.		the association of only using permanent hair dye during adolescence.	
		Ovarian Cancer		
White et al. 2021[39]	Prospective cohort involving 40,559 Sister Study participants aged 35-74 at enrollment (2003-2009), with a mean of 10 years of follow-up. Participants reported their personal hair dye use with the information of type (permanent, semi-permanent, temporary), color (dark, light), duration (no-use, 0-<10 years, ≥10 years), and frequency (no-use, ≤4 times/year, ≥4 times/year).	No positive association was observed between incident ovarian cancer (n = 241) with ever-use of permanent (HR 1.07, 95% CI: 0.82-1.39), semi-permanent (HR 1.17, 95% CI: 0.85-1.60) and temporary dyes (HR 0.75, 95% CI: 0.45-1.26). Findings were similar when ovarian cancer cases were limited to those confirmed by medical record: permanent HR was 1.07 (95% CI: 0.82-1.39), semi-permanent HR was 1.17 (95% CI: 0.85-1.60), and temporary dyes HR was 0.75 (95% CI: 0.45-1.26). More frequent use of hair dye or duration use was not associated with an increased risk of ovarian cancer compared to never use. HR was 1.07 (95% CI: 0.79-1.45) for use of frequency > 4 times/year, and HR was 1.06 (95% CI: 0.78-1.43) for use of duration ≥ 10 years. When ovarian tumors were stratified by serous versus non-serous type, ever-use of permanent hair dye was positively associated with non-serous tumors (HR 1.94, 95% CI 1.12-3.37), but inversely associated with serous (HR 0.65, 95% CI: 0.43-0.99) tumors (heterogeneity p = 0.002). Such results were not found in the use of semi-permanent or temporary dyes.	Models adjusted for race/ethnicity, education, BMI, age at menarche, parity, menopausal status, hormone therapy use, hysterectomy status, tubal ligation status, smoking, and alcohol use. The author indicated that ovarian cancer is a rare disease (only 241 cases were diagnosed from a 10-year follow-up, large cohort of over 50,000 US women); considering that the non-serous group includes clear cell, endometrioid, and mucinous carcinomas, as well as other histologic types with different etiologies, the authors stated the ovarian cancer subtype-stratified analyses were difficult to interpret.	++++
		Prostate Cancer		
Lim et al. 2022[65]	Prospective cohort study recruited 28,795 male smokers (aged 50-69 year) from 1985 to 1988 in Finland, with a 28-year follow-up.	During a 28-year period of observation, 2703 incident prostate cancer cases were diagnosed. At the time of baseline interview, 75 men reported hair dye use, and 13 of them were diagnosed with prostate cancer thereafter. Men who used hair dyes was associated with higher prostate cancer risk (HR 1.77, 95% CI: 1.03-3.05), compared with no use. Subgroup analysis showed the positive risk association for hair dye use was more prominent among men with a lighter natural hair color (light red, fair, or light brown) HR = 4.58 (95% CI: 1.70-12.29, n = 4), compared to men with dark natural color (dark brown or black) HR = 1.66 (95% CI: 0.81-3.38, n = 8). Subgroup analyses had very small number of exposed cases, which might result in low statistical power.	Models adjusted for age, smoking, and family history of prostate cancer. While lack of information on specific hair dye chemical compositions, a multicenter survey showed that hair dyes used in Finland in the 1990s contained 4-amino phenol and toluene-2,5-diamine or toluene-2,5-diamine sulfate. The authors indicated, misclassification of hair dye exposure may have occurred because it was only assessed during study enrollment, thus hair dye use could have changed over time (e.g., baseline users might decide to stop hair coloration but not reported such change).	+
		Uterine Cancer		
Chang et al. 2022[72]	Prospective cohort involving 33,947 Sister Study participants aged 35-74 who had a uterus at enrollment (2003-2009), with a mean of 10 years of follow-up. Details obtained for personal hair dye use included hair dyes type (permanent, semi-permanent, temporary), color (dark, light), duration (no-use, <5 years, 5-9 years, ≥10 years), and frequency of use (no-use, ≤4	Over a mean follow-up of 10.9 years, 378 uterine cancer cases were identified, who reported a diagnosis of endometrial cancer, uterine sarcoma, or other types of cancer in the uterus after enrollment. Use of any type of hair dye was not associated with uterine cancer risk. Permanent dyes: Ever-use (HR 0.90, 95% CI: 0.74-1.11; n = 185) Ever-use to others (HR 0.69, 95% CI: 0.42-1.14; n = 17)	Models adjusted for age, race/ethnicity, education, BMI, physical activity, oral contraceptive use duration, hormone replacement therapy, and age at menarche. Associations with use of body waves or hair permanents as a combined exposure were also examined: the results were negative (HR 1.01, 95% CI: 0.75-1.37; n = 53).	++++

Table 1. Cohort studies considered by the Panel.				
Author	**Study type/Methodology**	**Results**	**Adjustment/Note**	**Study scale***
	time, or >4 times in the past 12 months prior to baseline). Use of other hair products were also examined, such as straighteners, relaxers, pressing products, hair permanents or body waves.	Frequency ≤4 times (HR 0.79, 95% CI: 0.59-1.05; n = 64) Frequency >4 times (HR 0.98, 95% CI: 0.78-1.24; n = 121) Duration <5 years (HR 0.75,95% CI: 0.54-1.04; n = 48) Duration 5-9 years (HR 0.84, 95% CI: 0.61-1.15; n = 50) Duration≥10 years (HR 0.82, 95% CI: 0.64-1.05; n = 112) Semipermanent dyes: Ever-use (HR 0.94, 95% CI: 0.72-1.24; n = 64) Ever-use to others (HR 0.78, 95% CI: 0.40-1.51; n = 9) Frequency ≤4 times (HR 0.91, 95% CI: 0.63-1.29; n = 35) Frequency >4 times (HR 0.98, 95% CI: 0.67-1.44; n = 29) Duration <5 years (HR 0.93, 95% CI: 0.67-1.27; n = 49) Duration 5-9 years (HR 1.15, 95% CI: 0.78-1.70; n = 28) Duration≥10 years (HR 0.90, 95% CI: 0.60-1.35; n = 26) Temporary dyes: Ever-use (HR 1.25, 95% CI: 0.88-1.78; n = 36)		

* Based on the Rollison et al. (2006) scale[5]:
+: Assessed ever/never use;
++: Assessed the type of hair dye, or dye type plus dye color or duration, or with information on two or three other factors (color, frequency, duration), but no information on type;
+++: Assessed dye type, color, and frequency or duration of use;
++++: Assessed all four critical aspects: hair dye type, color, duration, and frequency of use

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
		Breast Cancer		
Kinlen et al. 1977[30]	Hospital based case-control study in Oxford, UK, including 191 cases and 561 age and sex matched controls, of which 73 cases and 213 controls had ever used hair dyes. Details obtained for hair dye use including type (permanent, semi-permanent), and duration of use (no-use, 1-10 years, 11-19 years, ≥20 years) (1975-1976)	A non-statistically significant increase in the relative risk of breast cancer in women who ever used hair dyes, compared with never used hair dyes (RR = 1.01). There was no evidence of an increasing risk for breast cancer with increasing duration of use of hair dyes or with use beginning more than four or over nine years (RR = 0.95) before diagnosis.	Models adjusted for age; 95% CI range value was not available for the estimated RR. Among women aged > 50 years, there was a significantly greater proportion of past or present smokers in hair dye users (63% of cases and controls combined) than in the non-users (43.5%).	++
Stavraky et al. 1979[31]	Hospital based case-control study consists of 50 women cases at a cancer treatment center with 100 hospitalized controls in London, Ontario, and 35 cases with 70 neighborhood controls in Toronto, Ontario. Questionnaire elicited detailed information on the dye type (permanent, semi-permanent), use duration, and frequency. (1976)	No evidence of a statistically significant relationship between hair dye use and cancer was observed. Specifically, the RRs of breast cancer for use of permanent hair dyes (at any time) were 1.30 (95% CI: 0.60-2.50) in London and 1.10 (0.50-2.40) in Toronto, respectively. The RRs for use of semi-permanent hair dyes were 1.70 (95% CI: 0.40-6.50) in London and 0.30 (0.10-1.70) in Toronto, respectively.	Logit analysis adjusted for smoking, family history of cancer, and age at first birth.	++

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
		Association between cancer risks with hair dyes use and other hair product use (such as hair spray, color rinse, and streaking) was also examined. No significant correlation was identified.		
Koenig et al. 1991[32]	Hospital based case-control study with 398 women cases and 90 randomly selected controls from a screening center in NYC. Details collected for hair dye use including type (permanent, semi-permanent, temporary), dye color (light, medium, dark), duration (different periods of reproductive life) and frequency use (no-use, 1-9 times, 10-49 times, 50-149 times, 150-1,825 times) (1977-1981)	Most subjects (77%) had used hair dye at least once, 38% of the subjects at least 100 times. No increase in the odds of breast cancer in women who ever used hair dyes, compared with never use (OR 0.80, 95% CI: 0.60-1.10). No evidence of a trend in risk was observed with increasing number of hair dye uses. For example, the ORs of permanent dye use at low frequency (1-9 uses) and high frequency (150-906 uses) were 0.90 (95% CI: 0.60-1.30) and 0.80 (95% CI: 0.50-1.20), respectively. The ORs of dark dye use at low frequency (1-9 uses) and high frequency (150-1825 uses) were 0.70 (95% CI: 0.40-1.40) and 0.80 (95% CI: 0.50-1.50), respectively.	Age was adjusted in all of the analyses (cases were older than randomly selected controls, as expected, since the controls were randomly selected in a medical center). The results showed personal hair dye use was unrelated to breast cancer risk, while additional data in the study indicated there was an increased risk (OR 3.0, 95% CI: 1.1-7.8) in women working as beautician for ≥ 5 years. Selection bias lied in this study, as subjects recruited from a screening medical center, who seek screening only if they were experiencing cancer like symptoms.	++++
Heikkinen et al. 2015[33]	Population based case-control study of breast cancer in Finland. There were 6567 cases and 21,598 age-matched controls (22-60 years old). Details collected for hair dye use included type (permanent, semi-permanent, temporary), the total number of hair dye episodes during life (no-use, 1-2 times, 3-9 times, 10-34 times, 35-89 times, ≥ 90 times), and frequency of dyeing (never, rarely, quite often, often). (2000-2007)	A large proportion of women reported ever-use of hair dye products, with rates increasing from 84% in women born before 1950 up to 92% in women born in or after 1960. The adjusted OR for hair dye use was 1.23 (95% CI: 1.11-1.36) when comparing ever vs never users. When analysis was stratified by hair dye type, ORs were 1.25 (95% CI: 1.12-1.39) 1.31 (95% CI: 1.17-1.46), and 1.32 (95% CI: 1.16 -1.52) for permanent, semi-permanent, and temporary dyes, respectively. In women born before 1950, an increased odds were noted (OR 1.28, 95% CI: 1.10-1.48). Early age at first dye (20-29) was associated with higher odds of breast cancer, comparing to women started dying at ≥40 years (OR 1.14, 95% CI: 1.05-1.25). The association was not observed in those started using hair dyes before the age 20 (OR 1.06, 95% CI: 0.96-1.16). An increased risk was seen in a pooled estimate (starting age <30 vs. ≥ 30): OR = 1.07 (95% CI: 1.01-1.14).	Multivariate model adjusted for birth year, parity, age at first birth, family history of breast cancer, menarche age, contraceptives use, physical activity, alcohol, BMI, and education. Statistically significant trend was observed (p = 0.005) when considering the cumulative number of hair dye use during life (ORs ranged from 1.07 to 1.31): OR = 1.07 (0.88-1.29) for 1-2 times/life OR = 1.19 (1.03-1.39) for 3-9 times/life OR = 1.28 (1.12-1.47) for 10-34 times/life OR = 1.31 (1.14-1.51) for 35-89 times/life OR = 1.25 (1.08-1.45) for ≥ 90 times/life Hair dye users reported more often ever-use of alcohol, with only 7% of them reporting never-use, compared to never-use of 27% among the non-hair dye users.	+++
Dianatinasab et al. 2017[34]	Hospital-based case-control study in Iran with 526 women cases and 526 randomly selected, age-matched controls. Information collected on hair coloring used at "regular bases"; the frequency and duration of hair dye use was unknown. (2014-2016)	The OR of breast cancer from hair dye use on a regular basis compared to no use was 1.93 (95% CI: 1.41-2.62). The results also showed multiple other factors contributed to the risk of breast cancer, such as life stress, occupation, marital age, age at first deliver, parity, birth interval, BMI, oral contraceptive usage, physical inactivity, and smoking.	The author stated multivariable model were adjusted for education, occupation, family history of breast cancer, smoking, BMI, physical exercise, birth weight, stressful life, sleep quality, X-ray, OC use, hair coloring, marital age, age at first delivery, parity, birth interval, breastfeeding, menarche age, menopause status, stressful life, sleep quality and regular bedtime. The author stated the results of this study found no association between cosmetics use and breast cancer (detailed data were not available).	+
Llanos et al. 2017[35]	Population-based case-control study of African American and European American women (aged 20-75 years), recruited in WCHS study in NYC and ten counties in NJ, USA. There were 2280 cases (1508 African American and 772 White) and 2005 controls (1290 African American and 715 White), matched on frequency, age and race.	There was no association between regular hair dye use and breast cancer risk, OR was 1.12 (95% CI: 0.95-1.32) and 1.07 (95% CI: 0.86-1.32) for African American and European American women, respectively. Specifically, among African American women, breast cancer risk was higher for dark shades use (OR 1.51, 95% CI: 1.20-1.90) and salon application of dyes (OR 1.26, 95% CI: 1.00-1.58). Other examined associations were shown below (the results were negative): OR = 1.06 (95% CI: 0.88-1.29) for frequency of use ≤ 2 times/year	Multivariable analysis adjusted for age, education, BMI, family breast cancer, and oral contraceptive use. The authors indicated limited statistical power to evaluate associations by ER status due to small samples of these cases in this study. Among European American women, no association between hair dye use and breast cancer incidence was observed:	++++

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
	Data collected on patterns of hair dye use included the age women started regularly using hair dye, annual frequency of use (no-use, ≤ 2 times, >2 times), dye colors (light, medium, dark), duration (no-use, 1-10 years, 11-20 years, >20 years), and typical application used (home-kit or salon). (2002-2008)	OR = 1.20 (95% CI: 0.94-1.54) for frequency of use > 2 times/year OR = 1.17 (95% CI: 0.96-1.42) for 1-10 years duration of use OR = 1.03 (95% CI: 0.81-1.31) for >10 years duration of use OR = 0.92 (95% CI: 0.71-1.9) for use of light color dye OR = 0.89 (95% CI: 0.68-1.16) for use of medium color dye OR = 0.97 (95% CI: 0.73-1.29) for home-kit use When breast cancer cases stratified by estrogen receptor status, among African American women, use of dark shades (OR = 1.72, 95% CI: 1.30-2.26) and higher frequency of use (OR = 1.36, 95% CI: 1.01–1.84) were associated with increased risk ER^+ disease, but not ER^- disease; among European American women, use of dark shades (OR = 1.54, 95% CI: 1.01-2.33) was associated with increased ER^+ disease. In addition, among European American women, dual use of hair relaxers and hair dyes (OR 2.40, 95% CI: 1.35-4.27) was associated with higher breast cancer incidence.	OR = 1.16 (95% CI: 0.89-1.50) for frequency of use ≤ 2 times/year OR = 0.99 (95% CI: 0.77-1.28) for frequency of use > 2 times/year OR = 1.14 (95% CI: 0.88-1.48) for 1-10 years duration of use OR = 1.03 (95% CI: 0.80-1.33) for >10 years duration of use OR = 0.97 (95% CI: 0.73-1.27) for use of light color dye OR = 1.09 (95% CI: 0.84-1.43) for use of medium color dye OR = 1.22 (95% CI: 0.87-1.73) for use of dark shades OR = 0.95 (95% CI: 0.71-1.27) for salon application of dyes OR = 1.20 (95% CI: 0.92-1.58) for home-kit use	
Rao et al. 2022[36]	2998 breast cancer cases (2227 African American and 771 European American women) aged 53.3± 10.6 years from WCHS and WCHFS studies, conducted in NYC and ten counties in NJ, USA. This was a case-only analysis (cases identified from the Llanos et al. 2017 study described above), aiming at examining whether hair dye and relaxers use was associated with more aggressive tumor features. Details collected for hair dye use included type (permanent, semi-permanent, temporary), frequency of use (no-use, ≤ 2 times/year, >2 times/year), dye colors (light, medium, dark), duration (no-use, ≤10 years, >10 years), and typical application used (home-kit, salon, or combination). (2001-2018)	Compared to salon application of permanent hair dye, home kit and combination (both salon and home kit) application were associated with increased odds of poorly differentiated tumors in the overall sample. Home kit (OR 2.22, 95% CI: 1.21-5.00) and combination application (OR 2.46, 95% CI: 1.21-5.00) of dyes were positively associated with poorly differentiated tumors among Black women, but not White women (home kit: OR 0.90, 95% CI: 0.45-1.81; combination: OR 2.05, 95% CI: 0.94-4.47). Duration of hair dye use (≤10 years, or >10 years) was not associated with tumor differentiation. Combined applications of permanent hair dyes and relaxers were associated with breast tumor features including higher tumor grade and larger tumor size.	Adjusted for family history of breast cancer, oral contraceptive use, education, BMI, age, race, and mode of detection (routine mammography or clinical/physical exam). The authors stated the current study did not assess the changes in hair dye and/or chemical relaxer/straightening product formulations over time might have impacted the observed risk estimates. Among European American women using hair dye for >10 years, there were lower odds of positive lymph node status (OR 0.46, 95% CI: 0.27-0.79), which was not observed among Black women.	++++
		Hematologic Cancer		
Zhang et al. 2004[40]	Population-based case-control study with 601 female NHL cases (aged 21-84 years), and 717 age-matched (±5 years) controls from Connecticut Tumor registry database. Exposure information of hair dye use included type (permanent, semi-permanent, temporary), total applications (no-use, <100, 100-200, >200), dye colors (light, dark), duration (no-use, <15years, 15-25 years, >25 years), age at first use (<25 years, ≥25 years) and years since first use (< 25, 25-35, >35). (1995-2021)	An increased risk of NHL was observed among women who reported use of hair dyes before 1980 (OR 1.3, 95% CI: 1.0-1.8). In comparison, no increased risk of NHL overall and by subtype was found among women who started using hair-coloring products in 1980 or later (OR 0.9, 95% CI: 0.7-1.3). Specifically, the ORs were 2.1 (95% CI: 1.0-4.0) for women using darker permanent hair dye for ≥25 years and 1.7 (95% CI: 1.0-2.8) for women who had more than 200 applications. Further stratified analysis by subtype of NHL showed that Follicular type (OR 1.9, 95% CI: 1.1-3.2), B-cell (OR 1.6, 95% CI: 1.2-2.3), and low-grade lymphoma (OR 1.6, 95% CI: 1.0-2.5) generally were associated with an increased risk with permanent hair dye uses prior to 1980.	Models were adjusted for age and family history of NHL in first-degree relatives. The author stated other variables, such as, race, education, smoking, alcohol consumption, and farming history, did not result in material changes in the observed associations, and thus not included in the final models. An increased risk of NHL was found only among women who started using hair dyes before 1980. No clear evidence of a dose-response with the total number of applications, use duration, or in the years since first use.	+++
Morton et al. 2007[41]	Population-based case-control study of NHL in the USA. There were 1321 cases (aged 20-74 years) and 1057 age-, sex-, race-, and residency-matched controls from Iowa, Los	There were no overall association between permanent, semi-permanent and temporary hair dye use and bladder cancer risk among women or men.	Models adjusted for sex, age, race, and residency. The study particularly focused on the use of permanent dye, with dark colors and use before 1980, when hair dye formulations	++++

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
	Angeles County, metropolitan Detroit, and metropolitan Seattle. Known HIV-positive cases were excluded. Detailed information on patterns of hair dye use included duration of use (1-4 years, 5-14 years, ≥15 years), annually use frequency (1-4 times, 5-7 times, ≥8 times), number of lifetime use (1-24 times, 25-99 times, ≥100 times), hair dye type (permanent, semi-permanent, temporary), intense tone (black, dark brown, dark blonde), and dye color (black, brown, red). Association between *NAT1* and *NAT2* genetic variation and NHL risk was further examined. (1998-2000)	Risk estimates were higher for use before 1980 than for use after 1980, particularly for use of permanent, intense tone (black, dark brown, dark blonde) products (<1980: OR = 1.6, 95% CI: 0.9-2.7; ≥1980: OR = 0.6, 95% CI: 0.4-1.1). In subgroup analysis, women with ≥ 100 lifetime applications had a significantly elevated OR of 1.4 (95% CI: 1.0-2.0). Increased risk was also observed in women who used permanent, intense color tone products for ≥15 years prior to 1980 (OR = 3.9, 95% CI: 1.2-12.5), but no consistent dose-response patterns were observed with frequency, duration, or total lifetime applications. Increased NHL risks associated with hair dye use before 1980 were observed among NAT2 rapid/intermediate acetylation phenotype, but not among NAT2 slow acetylation phenotype. For instance, for use of permanent, intense tone products, *NAT2* rapid/intermediate acetylators OR was 3.3 (95% CI: 1.3-8.6), while *NAT2* slow acetylators OR was 1.5 (95% CI: 0.6-3.6). Women with one or two copies of the *NAT1**10 allele also had higher increases in NHL risk associated with use of permanent dye (including dark color and intense tone products) prior to 1980 than women with no copies of the *NAT1**10 allele: *NAT1**10 allele OR = 2.5 (95% CI: 1.1-5.9) for permanent dye (any)	changed. The authors stated the current study's finding of the increased NHL risk was limited to women who used dark color or intense tone permanent hair dyes before 1980. No evidence of increased risk of NHL among women or men who began hair dye use after 1980. .	
Wong et al. 2009[42]	Hospital-based case-control study of AML in Shanghai, China. There were 722 confirmed AML cases and 1444 individually gender-age-matched patient controls at 29 hospitals in Shanghai, China. Information collected only on frequency of hair dye use (no-use, once every 6 months or less frequent, every 3 to 6 months, every 3 months or more often). (2003-2007)	There was no increase in the risk of personal use of hair dyes with AML-total (OR 0.98, 95% CI: 0.80-1.20), or its four subgroups: AML-RCA (OR 1.01, 95% CI: 0.72-1.40), APL (OR 1.01, 95% CI: 0.72-1.40), AML-MD (OR 0.83, 95% CI: 0.55-1.25), and AML-noc (OR 1.05, 95% CI: 0.75-1.46). In comparison, the study identified a number of risk factor for AML, such as smoking, particularly among the male subjects, as well as alcohol consumption and a low level of education.	Conditional logistic regression models considering the matching between cases and controls (gender and age) were used for the calculation. The study comprised subjects from 29 hospitals in Shanghai; the authors stated subjects might not be a representative sample of the entire patient population in Shanghai.	+
Wong et al. 2010[43]	Hospital-based case-control study consisting of 649 confirmed NHL cases and 1298 individually gender and age-matched patient controls at 25 hospitals in Shanghai, China. (2002-2003)	There was no increase in the risk of personal use of hair dyes with NHL-total (OR 0.93, 95% CI: 0.75-1.16), or any of its subtypes, such as B-Cell neoplasms (OR 0.94, 95% CI: 0.74-1.19), FL (OR 1.57, 95% CI: 0.72-3.46), and T/NK-Cell Neoplasms (OR 0.88, 95% CI: 0.48-1.61). For the subtype CLL/SLL, the authors reported a significantly lower risk associated with hair dye use with an OR of 0.37 (95% CI: 0.18-0.76).	The authors stated that they also examined NHL risk by frequency of hair dye use, and no trend or pattern was found, while the data were not shown.	+
Chang et al. 2010[44]	Hospital-based case-control study of white male residents of Iowa and non-metropolitan areas of Minnesota, with 622 pathologically confirmed cases NHL and 1245 age and state- matched controls (aged ≥30) (1980-1983) Hair dye users enrolled with hair dye use at least once a month for ≥1 year, or occupational exposure to hair dyes on any job held for ≥1 year.	Positive associations were observed between hair dye use and t(14;18)-negative NHL (OR 2.90, 95% CI: 1.60-5.00) and bcl-2 positive NHL (OR 2.20; 95% CI: 1.40-3.40), but not with t(14;18)-positive NHL (OR 1.30; 95% CI: 0.60-2.60) or bcl-2 negative NHL (OR 1.40; 95% CI: 0.50-3.80). The authors pointed out the number of hair dye exposed cases was small: n = 12 for t(14;18)-negative NHL cases and n = 20 for bcl-2 positive NHL cases.	Adjusting for age, state, and proxy (next-of-kin) status. FISH and IHC assays were applied to determine NHL t(14;18) and bcl-2 case-subtypes.	+
Lv et al. 2011[45]	Hospital-based case-control study of MDS. There were 403 diagnosed cases and 806 gender- and age-matched patient controls from 27 major hospitals in Shanghai, China.	Univariate analysis results showed hair dye users at frequency ≥2 times/year showed an elevated risk of all MDS (OR 1.46, 95% CI: 1.03-2.07), while multivariate analysis showed the OR was 1.31 (95% CI: 0.88-1.93), indicating that hair dye use (≥2 times/year) was a relative risk factor, not an independent risk factor.	Multivariate logistic regression analysis was applied to examine whether the effects of the following parameters on MDS risk were independent to each other: use of Chinese medicines, exposure to high-voltage power lines, new building/renovation,	++

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
	Information on hair dye use frequency (no-use, < 2 time/year, ≥2 times/year) and accumulative uses (no-use, < 70 times, ≥70 times) was collected. (2003-2006)	In univariate analysis, the ORs for hair dye users at frequency < 2 time/year and life time hair dye users were 1.24 (95% CI: 0.96-1.62) and 1.05 (95% CI: 0.68-1.63), respectively. The ORs for hair dye total lifetime use at < 70 times and ≥70 times were 1.28 (95% CI: 0.97-1.68) and 0.92 (95% CI: 0.34-2.51), respectively. Associations were also examined between hair dye use (frequency and duration) with MDS subtypes RAEB and RCMD, all results were negative.	benzene, pesticides, herbicides, gasoline, gules, tobacco smoking, alcohol intake, education. Based on univariate analysis results, the authors stated the trend test for number of hair dye users per year was statistically significant (p for trend = 0.02), however, the trend test for lifetime hair dye users did not attain statistically significant.	
Salem et al. 2014[46]	Hospital-based case-control study of lymphoproliferative cancers in Egypt. There were 130 cases (107 NHL and 23 CLL) and 130 age and sex-matched controls. (2011-2012)	No significant association was found between lymphoproliferative disorders and history of using hair dyes ($\chi^2 = 0.47$, $p > 0.05$).	This study aimed to assess pesticide exposure as a risk factor for lymphoproliferative disorders in adults while other risk factors were also examined including hair dye use. The chi-square (χ^2) test was used to determine whether there is an association between categorical variables.	+
Parodi et al. 2016[47]	Population-based case-control study of leukemia and NHL in Italy. There were 161 cases (120 lymphoid and 41 myeloid) and 84 randomly-selected controls among women in the population studied. Duration of hair dye use < 15 years vs ≥ 15 years was evaluated. (2002-2005)	Hair dye use for at least 15 years was associated with NHL (OR 2.3, 95% CI: 1.00-4.90, p for trend = 0.036), but hair dye use for less than 15 years was not associated with NHL (OR 1.40, 95% CI: 0.60-3.10). Leukemia was not associated with using hair dye for at least 15 years (OR 2.70, 95% CI: 0.90-7.90) or for less than 15 years (OR 2.70, 95% CI: 0.90-8.40). Further subtype analysis showed that among the total B cell malignancies, an increased risk was associated with hair dye use more than 15 years (OR 2.6, 95 % CI: 1.2-5.6, p for trend = 0.048), but not with use less than 15 years (OR 1.3, 95 % CI: 0.5-3.1).	Models were adjusted by age, gender and type of interview. The analysis was restricted to women in the population studies because too few of the men reported any hair dye use.	+
Arshad et al. 2018[48]	Hospital-based case-control study of leukemia in Pakistan with 25 adult leukemia cases and 50 gender- and marital status-matched controls, and 40 children cases and 80 age and gender- matched controls. Interviews were carried out face-to-face with adults and with the parents of the children. (2014)	Increased leukemia risk was observed among hair dye users. The un-adjusted OR was 4.14 (95% CI: 1.28-4.95) for adults who reported ever-use of hair dye and 4.60 (95% CI: 1.57-4.60) for children (whose parents reported children's ever use of hair dye during interview), respectively.	The author stated OR and 95% CI were calculated for different exposures using Epi info 7. No more details of statistical methods or models were provided. The study identified a number of other leukemia risk factors for adult subjects, such as exposure to chemical factory, a positive family history of leukemia, a positive trauma history, live-in radiation area, etc.	+
Gao et al. 2018[49]	Hospital-based case-control study of childhood leukemia in China with 958 cases (580 boys, 378 girls) and 785 controls (449 boys, 336 girls). Information on mothers' use of hair dye were collected, stratified by during pregnancy, during breastfeeding, and 3 months before pregnancy. (2008-2017)	Multivariable analysis indicated children whose mothers had exposure to hair dye during the breastfeeding (OR 13.56, 95% CI: 1.11-165.21) were at higher risk of developing leukemia than controls (p = 0.041). Mothers use of hair dye 3 months before pregnancy was not associated with risk of childhood leukemia (OR 0.26, 95% CI: 0.53-1.23). The OR for mothers' use of hair dye during pregnancy was 1, while numerical value for 95% CI was not available.	Non-conditional logistic regression analysis was applied for multivariate analysis to evaluate risk factors. This is a single medical center study. The study also identified many factors that can increase the risk of childhood leukemia, such as maternal age, smoking during pregnancy, abortion history, family history of malignant tumors, parents use of hair dye, using birth control pills before pregnancy, etc.	+
Rafieemehr et al. 2019[50]	Hospital-based case-control study of ALL in Iran with 125 cases (age <15 years) and 130 age-, gender-, and residence matched-controls. (2015-1018)	No significant association was found between patient mothers' use of hair dye during pregnancy and the risk of ALL (OR: 0.87, 95% CI: 0.32-2.37).	Logistic regression was used to estimate the risk.	+

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
Bladder Cancer				
Kogevinas et al. 2006[58]	A hospital-based case-control study in Spain with 152 women cases (age 67 ± 10.1 years) and 166 age-, gender-, and hospital-matched controls (age 67 ± 0.3 years). Detailed information on patterns of hair dye use included year first used (before or after 1970), type of dye (permanent and others), dye color (light or dark), frequency of use (no-use, <1 time every 3 months, once every 2 or 3 month, once every 2 or 3 months, ≥1 time/month), and type of application (self with or without gloves vs. hairdresser) lifetime cumulative exposure (no-se, ≤ 90 times, 91-210 times, 211-504 times, >504 times), and duration of use (no-use, ≤10 years, 11-24 years, 25-32 years, > 32 years). Multiplicative interactions between hair dye use and genotypes were further evaluated, including NAT1, NAT2, CYP1A2, GSTM1, GSTT1 and GSTP1. (1998-2001)	No increased risk was associated with use of any hair dye (OR 0.8, 95% CI: 0.5-1.4) or of permanent hair dyes (OR 0.8, 95% CI: 0.5-1.5). No significant increase in risk was observed for use hair dyes at least 10 times (OR 1.3, 95% CI: 0.8-2.2). There was no trend in risk seen with increasing exposure for duration of use, average use, or cumulative use. Selected ORs were showed below: OR = 1.2 (95% CI: 0.5-2.7) for hair dye use > 32 years OR = 0.6 (95% CI: 0.3-1.4) for hair dye use > 504 times OR = 0.6 (95% CI: 0.3-1.1) for average use > 1 time/month Genotype-specific analysis indicated among carriers of the NAT1*10 allele, use of permanent hair dyes was associated with a higher OR of 2.9 (95% CI: 0.7-11.6) compared to non-users. No interaction between polymorphisms in NAT2, GSTM1, GSTT1, GSTP1 or CYP1A2 with hair dye uses.	ORs were adjusted for age, region, and smoking status. The analysis was limited to women and based on small numbers.	++++
Shakhssalim et al. 2010[59]	Population-based case-control study of bladder cancer in Iran with 692 cases and 692 gender- and age- controls (262 women vs 1122 men in total). People used hair dye once or more in a year were considered as hair dye users. (2006)	Adjusted OR (men and women combined) for hair dye use and bladder cancer was 1.99 (95% CI: 1.04-3.82). However, when women and men were analyzed separately, no significant association with hair dye use and bladder cancer was reported (ORs values were not available).	The conditional logistic regression models were used, and OR was adjusted for smoking. The study also identified several other lifestyle factors had significant correlations with bladder cancer, such as smoking, opium use, and history of excessive analgesic use.	+
Koutros et al. 2011[60]	Population-based case-control study with 193 cases (911 male and 282 female) and 1,418 state-, gender-, and age-matched controls (1039 male and 378 female) in Maine, Vermont, and New Hampshire, USA. Detailed information on patterns of hair dye use included the age at first use, year first used (<1980, ≥1980), year last used (<1980, 1980-1989, 1990-1999, 2000+), age at first use, duration of use (no-use, <10 years, 10-19 years, 20-29 years. 30+ years), number of lifetime use (no-use, <50 times, 50-99 times, 100-199 times, 200+ times), type of dye (dark permanent, exclusive permanent, semi-permanent, temporary), depth of color (light blonde, medium/dark blonde, light brown, light red, med/dark brown, med/dark red), dye color (blonde, red, brown, black). Effect modification by NAT1, NAT2, GSTM1, and GSTT1 genotypes were further evaluated. (2001-2004)	There were no overall association between age at first use, year of first use, type of product, color, duration, or number of applications of hair dyes and bladder cancer risk among women or men. The ORs of ever hair dye use were 0.7 (95% CI: 0.5-1.0) among women and 0.7 (95% CI: 0.4-1.0) among men, respectively. Exclusive use of permanent hair dyes was not related to risk among women (OR 0.8, 95% CI: 0.5 -1.2) and men (OR 0.6, 95% CI: 0.3 -1.1). As for cumulative uses, selected ORs were presented below: OR = 1.4 (95% CI: 0.7-2.8) for exclusive permanent use > 30 years OR = 0.9 (95% CI: 0.4-1.7) for exclusive permanent use > 200+ times OR = 0.5 (95% CI: 0.2-1.4) for semi-permanent use > 30 years OR = 0.8 (95% CI: 0.4-1.8) for semi-permanent use > 200+ times Subgroup analysis identified an increased risk of bladder cancer (OR 3.3, 95% CI: 1.2-8.9) among women who had a college degree and used permanent dyes. Among all women, the interactions between genetic variants (NAT1, NAT2, GSTM1, and GSTT1) and hair dye use were not statistically significant.	Models adjusted for age, race, state, and smoking. Numbers of subjects in stratified analyses were often small, resulting in imprecise estimates, particularly in genotype /phenotype subgroups. In college educated women, an association was observed between permanent dye use and bladder cancer; while an inverse association was found among less educated women. The authors stated the observed qualitative interaction between permanent hair dye use and education may suggest that the increased risk observed among college educated women could be due to chance; in addition, these results need to be replicated to rule out the possibility of a false positive result from the multiple tests of interaction. There was an observed increased risk of bladder cancer associated with permanent hair dye use among college educated women with GSTT1-active genotypes compared to GTTT1 null genotypes (OR 5.9, 95% CI: 1.7-20.0); however, the author stated it may be a chance association due to the lack of evidence for the presence	++++

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
		In the subgroup of women with college degree, an increased risk of bladder cancer was observed among exclusive permanent hair dye users who had NAT2 slow acetylation phenotype (OR 7.3, 95% CI: 1.6 -32.6), compared to never users of dye who had NAT2 rapid/intermediate acetylation phenotype. But the authors stated the interaction was not statistically significant (such analysis was based on 15 cases and 6 controls).	of GSTT1-metabolized conjugated mutagenic intermediates in hair dyes and the low prevalence of GSTT1 null genotype.	
Ros et al. 2012[61]	Population-based case-control study in the Netherlands, with 1385 cases (246 women) and 4754 age- and sex-matched controls (2587 women). Detailed information on patterns of hair dye use included dye entire or part of hair, dye color (Blond, brown, black, red and other), lifetime use (no-use, ≤40 times/life, >40 times/life), duration of use (no-use, ≤10 years, >10 years). Bladder cancer subtype was stratified by aggressive cancer or non-aggressive cancer. (1975-2009)	No association was observed between bladder cancer risk and use of permanent hair dye (OR 0.87, 95% CI: 0.65-1.18) and temporary dye (OR 0.7, 95% CI: 0.58-1.02). No association was found when patients were stratified by prognostic subtype of bladder cancer: aggressive (OR 0.50, 95% CI: 0.24-1.05) vs. non-aggressive (OR 0.68, 95% CI: 0.37-1.24). No association was found between bladder cancer risk and duration of hair dye use, number of times used per year, total number of times used over a lifetime, dying all the hair or only part of the hair, or dye color (none of the subjects reported use of black dye). Selected ORs were presented below: OR = 0.86 (95% CI: 0.55-1.35) for exclusive permanent use >40 times OR = 0.78 (95% CI: 0.33-1.83) for exclusive permanent use >5 times/year OR = 0.91 (95% CI: 0.57-1.46) for exclusive permanent use >10 year OR = 0.86 (95% CI: 0.56-1.31) for dye entire hair (exclusive permanent) OR = 0.86 (95% CI: 0.50-1.50) for brown color (exclusive permanent)	All analyses were adjusted for age and smoking (duration and intensity). Analyses were not performed for the men selected for the study because less than 5% reported ever using hair dyes.	++++
Brain Cancer				
Holly et al. 2002[63]	Population-based case-control study conducted in the west coast of the USA (Los Angeles, San Francisco, and Seattle), with 540 CBT cases (<20 years) and 801 birth- and sex-matched controls. Subjects' mothers reported hair dye use (permanent, semi-permanent, temporary) before and during pregnancy (used intermittently vs. used continuously; used 1 month before conception or in first/second/third trimester). (1984-1991)	Overall, exclusive use of permanent dye, semi-permanent, temporary dye or hair darkeners before or during pregnancy was not associated with risk for CBT. Selected ORs were presented below: OR = 0.96 (95% CI: 0.69-1.3) for ever-use hair dye during pregnancy or 1 month before conception OR = 1.40 (95% CI: 0.88-2.3) for continuous use OR = 0.88 (95% CI: 0.60-1.3) for permanent dye use 1 month before and/or during pregnancy OR = 2.50 (95% CI: 0.58-10) for semi-permanent dye 1 month before conception Risks for the three major subtypes of CBT, astrocytic tumors (OR 1.00, 95% CI: 0.69-1.5), PNET (OR 0.97, 95% CI: 0.51-1.9) and other gliomas (OR 0.76, 95% CI: 0.40-1.4), were not associated with the use of hair dyes during pregnancy.	Age- and sex-adjusted unconditional logistic regression analyses were performed. Interviews on mothers' use of hair dye were conducted up to 20 years after the index children's birth, thus reports of exposures regarding type of hair dye and frequency of use by trimester may not be accurate.	+++

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
		Prostate Cancer		
Tai et al. 2016[66]	Hospital-based case-control study of prostate cancer in Taiwan with 296 cases and 296 age-, ethnicity-, and hospital-matched controls from 2 large medical centers in Southern Taiwan. Another 608 incident prostate cancer cases were investigated to determine the rate of prostate cancer survival. Detailed information on patterns of hair dye use included age of first use, duration of use (no-use, ≤10 years, >10 years), frequency (no-use, ≤6 times /year, >6times/years), year of first use (after or before 1980). (2000-2007)	The prevalence of hair dye use was higher in the cases than the controls (95/296 = 32.1% vs. 64/296 = 21.6%, $p < 0.05$), and the hair dye users had increased odds of prostate cancer when compared with the non-users (OR 2.15, 95% CI: 1.32-3.57). The increased risk was observed in patients who started to use hair dye products before 1980 (OR 2.16, 95% CI: 1.28-3.68), but not in those started to use after 1980 (OR 0.89, 95% CI: 0.11-5.90). The authors stated dose-response effects of increased exposure duration and frequency were observed ($p_{trend} < 0.01$). The relevant ORs were shown below: OR = 1.57 (95% CI: 0.82-3.03) for duration of use ≤ 10 years OR = 2.54 (95% CI: 1.23-5.41) for duration of use >10 years OR = 1.73 (95% CI: 0.91-3.32) for frequency of use ≤ 6 times/year OR = 2.65 (95% CI: 1.26-5.78) for frequency of use > 6 times/year In the survival analysis, of the 608 cases, 26.4% (161/608) reported having used hair dyes. The use of hair dye did not affect cumulative incidence estimates of prostate cancer-specific deaths (p = 0.753).	Models adjusted for age, marital status, blood type, education, family history of prostate cancer, smoking, alcohol consumption, and betel nut chewing. Although the color of hair dyes was not included in questionnaires, the author stated most people use black or dark hair dyes in Taiwan.	++
		Pediatric Germ Cell Tumors		
Lin et al. 2020[69]	Hospital-based case-control study with 42 GCT cases and 42 sex- and age-matched controls from Xinhua Hospital in Shanghai, China. Information on subject mothers' exposure to hair dye included frequency of use during pregnancy (no-use, <1 time/month, 1-4 times/month, ≥1/week). (2014-2017)	All participants with a history of hair dye usage during pregnancy had significantly elevated serum PFHxS levels compared with those without in the GCT [2.38 (1.72–3.29) ng/mL vs. 1.37 (0.63–1.95) ng/mL, p = 0.010] or control group [0.49 (0.34–0.67) ng/mL vs. 0.32 (0.19–0.46) ng/mL, p = 0.020]. Logistic regression analysis further identified PFHxS levels were statistically significantly associated with GCTs. The OR for a 1 ng/L increase of PFHxS in serum was 19.47 (95% CI: 4.20 - 90.26). The authors concluded serum PFHxS levels were independently associated with GCT occurrence.	Models adjusted for infectious disease, cosmetics usage, barbecued food consumption, filtered water use, indoor decorating, living near farmland. The results of the study indicated parental consumption of barbecued foods during pregnancy was also significantly correlated with increased serum PFHxS levels in both GCT and control groups.	++
		Testicular Cancer		
Ghazarian et al. 2018[70]	Population based case-control study of TGCT in the US with 527 mothers of TGCT cases and 562 mothers of age-, and race--matched controls in US STEED study. Information on frequency of hair dye use in mothers were collected (≤ once/week vs. > once/week). (2002-2005)	Maternal use of hair dye (OR 0.80, 95% CI: 0.54-1.18), hairspray (OR 1.17, 95% CI: 0.89-1.55), or permanent wave (OR 1.18, 95% CI: 0.86-1.62) during pregnancy and breastfeeding was not associated with TGCT risk in sons.	Models adjusted for maternal age at delivery, race, duration of product use, weight gain during pregnancy, son's age at diagnosis, family history of TGCT, and cryptorchidism.	+
		Salivary Gland Cancer		
Spitz et al. 1990[25]	Hospital-based case-control study of salivary gland cancers in Houston, with 64 cases and 128 sex-, race- and ethnicity-matched controls from MD Anderson Cancer center. Randomly selected controls excluded patients with cancer of the head and neck or nonmelanoma skin cancer.	Ever-use of hair dye was not associated with increased risk of salivary gland cancer. The OR was 2.3 (95% CI: 0.9-6.2) and 3.5 (95% CI: 0.9-12.8) for hair dye use ≤ 15 years or >15 years, respectively. Subgroup analysis indicated hair dye use was significantly related to salivary gland cancers risk in women (OR 2.5, 95% CI: 1.2-5.2).	Multiple logistic regression analysis was performed on univariate risk factors, including higher education, alcohol consumption, prior radiotherapy, and mouthwash, and hair dye use.	+

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
	Information on duration of hair dye use in men and women subjects were collected (≤ 15 years vs. >15 years). (1985-1989)			
		Genetic Polymorphism		
Koutros et al.2011[60]	Population-based case-control study with 193 bladder cancer cases (911 male and 282 female) and 1418 state-, gender-, and age-matched controls (1039 male and 378 female) in Maine, Vermont, and New Hampshire, USA. Detailed information on patterns of hair dye use included the age at first use, year first used (<1980, ≥1980), year last used (<1980, 1980-1989, 1990-1999, 2000+), age at first use, duration of use (no-use, <10 years, 10-19 years, 20-29 years. 30+ years), number of lifetime use (no-use, <50 times, 50-99 times, 100-199 times, 200+ times), type of dye (dark permanent, exclusive permanent, semi-permanent, temporary), depth of color (light blonde, medium/dark blonde, light brown, light red, med/dark brown, med/dark red), dye color (blonde, red, brown, black). Effect modification by NAT1, NAT2, GSTM1, and GSTT1 genotypes were further evaluated. (2001-2004)	There were no overall association between age at first use, year of first use, type of product, color, duration, or number of applications of hair dyes and bladder cancer risk among women or men. The ORs of ever hair dye use were 0.7 (95% CI: 0.5-1.0) among women and 0.7 (95% CI: 0.4-1.0) among men, respectively. Exclusive use of permanent hair dyes was not related to risk among women (OR 0.8, 95% CI: 0.5 -1.2) and men (OR 0.6, 95% CI: 0.3-1.1). As for cumulative uses, selected ORs were presented below: OR = 1.4 (95% CI: 0.7-2.8) for exclusive permanent use > 30 years OR = 0.9 (95% CI: 0.4-1.7) for exclusive permanent use > 200+ times OR = 0.5 (95% CI: 0.2-1.4) for semi-permanent use > 30 years OR = 0.8 (95% CI: 0.4-1.8) for semi-permanent use > 200+ times Subgroup analysis identified an increased risk of bladder cancer (OR 3.3, 95% CI: 1.2-8.9) among women who had a college degree and used permanent dyes. Among all women, the interactions between genetic variants (NAT1, NAT2, GSTM1, and GSTT1) and hair dye use were not statistically significant. In the subgroup of women with college degree, an increased risk of bladder cancer was observed among exclusive permanent hair dye users who had NAT2 slow acetylation phenotype (OR 7.3, 95% CI: 1.6-32.6), compared to never users of dye who had NAT2 rapid/intermediate acetylation phenotype. But the authors stated the interaction was not statistically significant (such analysis was based on 15 cases and 6 controls).	Models adjusted for age, race, state, and smoking. Numbers of subjects in stratified analyses were often small, resulting in imprecise estimates, particularly in genotype /phenotype subgroups. In college educated women, an association was observed between permanent dye use and bladder cancer; while an inverse association was found among less educated women. The authors stated the observed qualitative interaction between permanent hair dye use and education may suggest that the increased risk observed among college educated women could be due to chance; in addition, these results need to be replicated to rule out the possibility of a false positive result from the multiple tests of interaction. There was an observed increased risk of bladder cancer associated with permanent hair dye use among college educated women with GSTT1-active genotypes compared to GTTT1 null genotypes (OR 5.9, 95% CI: 1.7-20.0); however, the author stated it may be a chance association due to the lack of evidence for the presence of GSTT1-metabolized conjugated mutagenic intermediates in hair dyes and the low prevalence of GSTT1 null genotype.	++++
Gago-Dominguez et al. 2003[73]	A population-based case-control study, with 159 women cases and 164 sex-, race-, age-, and residency-matched controls. Information on hair dye uses included type (permanent, semi-permanent, temporary), cumulative use (<100 times or 100+ times), frequency (no-use, <12 times/year or 12+ times/year) and duration of uses (no-use, <15 years or 15+ years). Modifying effects of genotypes/phenotypes (GSTM1, GSTT1, GSTP1, NAT1, NAT2, CYP1A2) on the permanent hair dye-bladder cancer association were evaluated. (1992-1996)	Women with the NAT2 slow-acetylator phenotype who exclusively used permanent hair dyes had an increased risk of bladder cancer (OR 2.90, 95% CI: 1.30 - 7.50) after adjustment for cigarette smoking, compared to individuals with the NAT2 rapid-acetylator phenotypes (OR 1.30, 95% CI: 0.60-2.80). Women with a NAT1*10 genotype who were non-smokers and used permanent hair dyes exclusively had an OR of 1.00 (95% CI: 0.20-4.30), and those with a non-NAT1*10 genotype had an OR of 6.80 (95% CI: 1.70-27.40) in this study. Statistically significant associations between permanent hair dye use and bladder cancer risk were observed among subjects exhibiting the NAT 2 slow phenotype, NAT1*10 genotype, or slow CYP1A2 phenotype (p for trend < 0.05, for duration of use, frequency of use, and cumulative lifetime use, respectively). No difference was seen in risk of bladder cancer from permanent hair dye exposure when subjects were stratified by genotypes of NAT1, GSTM1, GSTT1, or GSTP1.	ORs were adjusted for smoking (intensity and duration), age, and ethnicity. The modifying effect of the *NAT1* genotype is absent among smokers. The reason might be, according to the authors, the smokers were exposed chronically to 4-aminobiphenyl, an aromatic amine present in cigarettes that can own-regulate NAT1 in skin.	+++
Kogevinas et al. 2006[58]	A hospital-based case-control study in Spain with 152 women cases (age 67 ± 10.1 years) and 166 age-, gender-,	No increased risk was associated with use of any hair dye (OR 0.8, 95% CI: 0.5-1.4) or of permanent hair dyes (OR 0.8, 95% CI: 0.5-1.5). No significant increase in risk	ORs were adjusted for age, region, and smoking status.	++++

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
	and hospital-matched controls (age 67 ± 0.3 years). (1998-2001) Detailed information on patterns of hair dye use included year first used (before or after 1970), type of dye (permanent and others), dye color (light or dark), frequency of use (no-use, < 1 time every 3 months, once every 2 or 3 month, once every 2 or 3 months, ≥ 1 time/month), and type of application (self with or without gloves vs. hairdresser) lifetime cumulative exposure (no-use, ≤ 90 times, 91-210 times, 211-504 times, >504 times), and duration of use (no-use, ≤ 10 years, 11-24 years, 25-32 years, > 32 years). Multiplicative interactions between hair dye use and genotypes were further evaluated, including NAT1, NAT2, CYP1A2, GSTM1, GSTT1 and GSTP1.	was observed for use hair dyes at least 10 times (OR 1.3, 95% CI: 0.8-2.2). There was no trend in risk seen with increasing exposure for duration of use, average use, or cumulative use. Selected ORs were showed below: OR = 1.2 (95% CI: 0.5-2.7) for hair dye use > 32 years OR = 0.6 (95% CI: 0.3-1.4) for hair dye use > 504 times OR = 0.6 (95% CI: 0.3-1.1) for average use > 1 time/month Genotype-specific analysis indicated among carriers of the NAT1*10 allele, use of permanent hair dyes was associated with a higher OR of 2.9 (95% CI: 0.7-11.6) compared to non-users. No interaction between polymorphisms in NAT2, GSTM1, GSTT1, GSTP1 or CYP1A2 with hair dye uses.	The analysis was limited to women and based on small numbers.	
Morton et al. 2007[41]	Population-based case-control study of NHL in the USA. There were 1321 cases (aged 20-74 years) and 1057 age-, sex-, race-, and residency-matched controls from Iowa, Los Angeles County, metropolitan Detroit, and metropolitan Seattle. Known HIV-positive cases were excluded. Detailed information on patterns of hair dye use included duration of use (no-use, 1-4 years, 5-14 years, ≥15 years), annually use frequency (no-use, 1-4 times, 5-7 times, ≥ 8 times), number of lifetime use (no-use, 1-24 times, 25-99 times, ≥100 times), hair dye type (permanent, semi-permanent, temporary), dye color (black, brown, red), intense tone (black, dark brown, dark blonde), dye color (blonde, red, brown, black). Association between NAT1 and NAT2 genetic variation and NHL risk was further examined. (1998-2000)	There were no overall association between permanent, semi-permanent and temporary hair dye use and bladder cancer risk among women or men. Risk estimates were higher for use before 1980 than for use after 1980, particularly for use of permanent, intense tone (black, dark brown, dark blonde) products (<1980: OR = 1.6, 95% CI: 0.9-2.7; ≥1980: OR = 0.6, 95%CI: 0.4-1.1). In subgroup analysis, women with ≥ 100 lifetime applications had a significantly elevated OR of 1.4 (95% CI: 1.0-2.0). Increased risk was also observed in women who used permanent, intense color tone products for ≥15 years prior to 1980 (OR = 3.9, 95% CI: 1.2-12.5), but no consistent dose-response patterns were observed with frequency, duration, or total lifetime applications. Increased NHL risks associated with hair dye use before 1980 were observed among NAT2 rapid/intermediate acetylation phenotype, but not among NAT2 slow acetylation phenotype. For instance, for use of permanent, intense tone products, *NAT2* rapid/intermediate acetylators OR was 3.3 (95% CI: 1.3-8.6), while *NAT2* slow acetylators OR was 1.5 (95% CI: 0.6-3.6). Women with one or two copies of the *NAT1*10* allele also had higher increases in NHL risk associated with use of permanent dye (including dark color and intense tone products) prior to 1980 than women with no copies of the *NAT1*10* allele: *NAT1*10* allele OR = 2.5 (95% CI: 1.1-5.9) for permanent dye (any)	Models adjusted for sex, age, race, and residency. The study particularly focused on the use of permanent dye, with dark colors and use before 1980, when hair dye formulations changed. The authors stated the current study's finding of the increased NHL risk was limited to women who used dark color or intense tone permanent hair dyes before 1980. No evidence of increased risk of NHL among women or men who began hair dye use after 1980. .	++++
Zhang et al. 2009[74]	A population-based case-control study with 461 female NHL cases (aged 21-84 years), and 535 age-matched (±5 years) controls who provided blood samples for genotype analysis. Cases were identified from Connecticut Tumor Registry database (same study population was examined in Zhang et al. 2004[40]) (1996-2022)	None of the different individual genes examined was associated with a statistically significant change in the risk of NHL for any of the NHL subtypes considered, except FL (a major subtype of NHL). Among women who started using hair dye before 1980 as compared with never users, a statistically significantly increased risk of NHL was found for carriers of CYP2C9 Ex3-52C>T TT/CT genotypes (OR 2.9, 95% CI: 1.4-6.1), CYP2E1 -332T>A AT/AA genotypes (OR 2.0, 95% CI: 1.2- 3.4), a homozygous or heterozygous 3-base-pair deletion in intron 6 of GSTM3 (OR 2.3, 95% CI: 1.3- 4.1), GSTP1 Ex5-24A>G AA genotypes (OR 1.8, 95% CI: 1.1-2.9), or NAT2 genotypes conferring intermediate/rapid acetylator status (OR 1.6, 95% CI: 1.0-2.7).	Analyses were adjusted for age and race. The author stated other variables, such as smoking, alcohol consumption, and farming history, did not result in material changes in the observed associations, and thus not included in the final models. No effect modifications were found for women who started using hair dyes in 1980 or later. A total of 19 single nucleotide polymorphisms in 9 xenobiotic genes were genotyped, including CYP1A1 (rs1048943), CYP1A2 (rs762551), CYP1B1(rs1056836), CYP2C9 (rs1799853), CYP2E1 (rs2070673 and rs2031920), GSTM3 (rs1799735), GSTP1 (rs1695	+++

Table 2. Case-control studies considered by the Panel.				
Author	**Study type/Methodology (diagnosis period)**	**Results**	**Adjustment/Note**	**Study scale***
		In contrast, no significantly increased risk was observed for starting hair dye use before 1980 (relative to never use) among women who were homozygous wild-type for the CYP2C9, CYP2E1, or GSTM3 polymorphisms, women carrying 1 or 2 copies of the variant GSTP1 allele, or women who were slow NAT2 acetylators.	and rs1138272), NAT1 (rs4987076, rs13249533, rs1057126, and rs15561), and NAT2 (rs1041983, rs1801280, rs1799929, rs1799930, rs1208, and rs1799931).	
Guo et al. 2014[76]	518 female NHL cases and 597 controls identified from Connecticut Tumor Registry database (same study population was examined in Zhang et al. 2004[40]). 24 single nucleotide polymorphisms in 16 DNA repair genes were examined. (1996-2000)	No associations for hair dye use before 1980 with risk of DLBCL were observed when stratifying by the genotypes for any of the 24 SNPs. The following 10 genotypes in combination with hair dye use before 1980 were associated with FL risk: BRCA2 rs144848 AC+CC (OR = 3.28, 95 % CI: 1.27-8.50) WRN rs1346044 TT (OR = 2.70, 95 % CI: 1.30-5.65) XRCC3 rs861539 CT+TT (OR = 2.76, 95 % CI: 1.32-5.77) XRCC4 rs1805377 GG (OR = 2.07, 95 % CI:1.10-3.90) rs1056503 TT (OR = 2.17, 95 % CI:1.16-4.07) ERCC1 rs3212961 CC (OR = 1.93, 95 % CI:1.00-3.72) RAD23B rs1805329 CC (OR = 2.28, 95 % CI:1.12-4.64) MGMT rs12917 CC (OR = 1.96, 95 % CI:1.06-3.63) rs2308321 AA (OR = 2.02, 95 % CI:1.09-3.75) rs2308327 AA genotypes (OR = 2.23, 95 % CI:1.16-4.29) A significant interaction with risk of overall NHL was observed between WRN rs1346044 and hair dye use before 1980 (p = 0.032).	Models were adjusted for age, race, and smoking status. No sufficient cases for analyzing NHL subtypes of CLL/SLL and MZBCL. There was no association between NHL, FL, or DLBCL in women who began using hair dyes after 1980.	+++

* Based on the Rollison et al. (2006) scale[5]:
+: Assessed ever/never use;
++: Assessed the type of hair dye, or dye type plus dye color or duration, or with information on two or three other factors (color, frequency, duration), but no information on type;
+++: Assessed dye type, color, and frequency or duration of use;
++++: Assessed all four critical aspects: hair dye type, color, duration, and frequency of use

Table 3. Meta-analysis studies considered by the Panel			
Author	**Study involved (Published period)**	**Results**	**Note**
		Breast Cancer	
Takkouche et al. 2005[24]	12 case-control studies (5019 cases and 8486 controls), and 2 cohort studies (665,993 participants with 1135 breast cancer cases). (1977-2002)	The random-effects pooled RR of breast cancer for any type of dye was 1.06 (95% CI: 0.95-1.18). The pooled RR for exclusive use of permanent dye was 1.00 (95% CI: 0.94-1.05), and was 0.99 (95% CI, 0.89-1.11) for intensive exposure (≥ 200 times). There was no substantial difference in pooled RRs across study designs (2 cohort, 7 hospital-based case-control, and 5 population-based case-control studies).	When information in the publications were missing, the authors assumed an average frequency of hair dyeing of 11.7 times/year among women. Heterogeneity of the study specific RRs was moderate to large for case-control studies (study variance Ri = 0.62), 1.20), and all studies analyzed together (Ri = 0.68).
Gera et al. 2018[37]	8 case-control studies with 11,079 cases and 26,958 controls (conducted in Iran, Finland, and USA). (1980-2017)	In a random-effects model, the pooled RR for breast cancer risk following hair dye exposure was 1.15 (95% CI: 0.996 -1.319). The adjusted combined effect according to the Duval and Tweedie's Trim and Fill procedure (adjust for publication bias) revealed a RR of 1.18 (95% CI: 1.03 -1.37).	Of the 24 studies initially considered relevant, 5 prospective studies, which did not show any association between hair dye use and breast cancer, were excluded in the final meta-analysis The author stated the reliability of this statistical analyses has decreased because of the large number of excluded prospective studies. The authors stated there was significant heterogeneity among studies involved in the meta-analysis, and no uniform adjustment for confounding factors were conducted across studies.
Xu et al. 2021[38]	11 case-control studies (44,614 subjects) and 3 prospective cohort studies (165,785); subjects from the North America, Asia, Europe, and Australia. (1978-2019)	A slightly increased breast cancer risk was found in hair dyes users (random-effect pooled OR = 1.07; 95% CI: 1.01-1.13). Specifically, with permanent hair dye use OR = 1.08 (95% CI: 1.03-1.14), with semi-permanent hair dye use OR = 1.09 (95% CI: 0.92-1.28), with rinse (temporary) hair dye use OR = 1.17 (95% CI: 1.0 -1.35), and with straightener use OR= 1.04 (95% CI: 0.96 - 1.14). No impact was identified on the overall correlation between hair dyes and breast cancer risk when subjects were stratified by race (White vs. non-White: pooled OR = 1.05; 95% CI: 0.86-1.29), duration of use (<10 years vs. ≥10 years: pooled OR = 0.96; 95% CI: 0.85-1.08) or dye color (dark vs. light: pooled OR = 0.91; 95% CI: 0.62-1.32).	For studies included, the most common nation of origin was the USA (9 studies). Only English publications were included, and the authors stated that nearly 50% of included studies were at high risk of selection bias. As the authors pointed out, clinical heterogeneity might result from differences in the chemical formulations of hair care products, dyeing frequency and the breast cancer family history of analyzed subjects across all included studies. The random-effect model was adopted for the following meta-analyses due to the heterogeneity: hair dyes and breast cancer risk, rinse and breast cancer risk, semipermanent hair dye and breast cancer risk, White vs non-White and lighter vs darker.

Table 3. Meta-analysis studies considered by the Panel			
Author	**Study involved (Published period)**	**Results**	**Note**
		Hematologic Cancer	
Takkouche et al. 2005[24]	31 case-control studies (8565 cases and 13,641 controls), and 9 cohort studies (672,436 participants with 712 cases). (1981-2005)	When all hematopoietic cancers were combined, including NHL, HL, multiple myeloma, and leukemia, the pooled RR for ever-users of hair dye was 1.15 (95% CI, 1.05-1.27). The increased risk is restricted to case-control studies (pooled RR 1.23, 95% CI: 1.09-1.39); in comparison, no risk increase was observed when all cohort studies were combined (pooled RR 1.01, 95% CI: 0.89-1.16). More specifically, the increase in case-control studies is restricted to the 17 case-control studies with data on men (pooled RR 1.57, 95% CI: 1.33-1.84). No risk was observed when analysis focused on women (RR 1.04, 95% CI: 0.97-1.11), or to exclusive use of permanent dyes (≥200 times) in both men and women (random-effects pooled RR 1.14, 95% CI: 0.99-1.29). Additionally, the results of intensive exposure did not show any association between hair dyes exposure and hematopoietic cancers (RR 1.12, 95% CI: 0.98-1.28).	Adjustment for smoking did not affect the results. The funnel plot for measuring publication bias showed substantial asymmetry (p = 0.02). The author stated in their analysis, several case-control studies used the same comparison group for different outcomes, which could result in finding more statistically significant associations than they actually exist. The authors further pointed out such multiple comparison issue may partially explain the positive results for hematopoietic cancers.
Zhang et al. 2008[51]	4 case-control studies (4461 cases and 5799 controls); all studies were included in the InterLymph project. (1988-2003)	Increased risk of NHL (pooled OR 1.3, 95% CI: 1.1 - 1.4) was observed among women who began using hair dye before 1980, but not among women who started use in 1980 or later (pooled OR 1.1, 95% CI: 0.9 - 1.2). Further stratified analyses by NHL subtype were conducted in subjects who started using hair dyes before 1980. The results indicated increased risk for FL (OR 1.4, 95% CI: 1.1 - 1.9) and CLL/SLL (OR 1.5, 95% CI: 1.1 - 2.0) but not for other NHL subtypes. Risk of NHL was not associated with hair-dye use before or after 1980 among men.	The final model was adjusted for age, gender, race (White, Black, or other), and study center. The current analysis investigated the relation between hair dye use and NHL risk in separating persons who started using hair dyes before 1980, compared to those who started using hair dyes in 1980 or later.
Linet et al. 2014[52]	19 case-control studies (3530 FL cases and 22,639 controls); all studies were included in the InterLymph NHL Subtypes Project, and conducted in Europe, North America, and Australia. (1991-2011)	FL risk was examined in females only. No associations between FL and hair dye use type, duration, or frequency were found in this study (data not shown in the study), except for a modest increase in women who used hair dyes before 1980 (adjusted OR 1.40, 95% CI: 1.10-1.78).	Age-, race/ethnicity-, sex- and study-adjusted ORs and 95% CI were estimated using logistic regression. The analysis evaluated many risk factors for FL, such as medical history, lifestyle, and family history of cancer.

Table 3. Meta-analysis studies considered by the Panel			
Author	**Study involved (Published period)**	**Results**	**Note**
Cerhan et al. 2014[53]	19 case-control studies (4667 DLBCL cases and 22,639 controls), Studies were included in the InterLymph project, and conducted in Europe, North America, and Australia. (1991-2011)	There were no overall and sex- or age-specific associations between DLBCL and hair dye use, based on the basic adjusted model results of this study. The pooled OR of mediastinal DLBCL was 4.97 (95% CI: 1.63-15.15) for use of hair dyes for at least 20 years, compared with non-use. Pooled ORs were 0.58 (95% CI: 0.21-1.62) and 0.15 (95% CI: 0.02-1.22) for use of hair dyes for 1-8 years and 9-19 years, respectively. Using hair dyes for ≥ 20 years was not associated with DLBCL at other anatomical sites, including CNS, testis, gastrointestinal tract, and skin. Use of hair dyes for < 20 years was not associated with DLBCL at any site. In comparison, smoking was associated with CNS, testicular and cutaneous DLBCLs in this study. When analysis stratified by ever hair dye us before or after 1980, there was no associated risk with DLBCL was identified: OR = 2.75 (95% CI: 0.91-8.29) for ever hair dye use <1980 OR = 0.56 (95% CI: 0.22-1.45) for hair dye use only ≥1980	HIV-associated DLBCL was excluded in the analysis. Unconditional logistic regression models were used to estimate OR and 95% CI with each exposure variable, adjusted for age, sex, race/ethnicity, and study ("basic adjusted models"). The authors indicated the results were not adjusted for multiple comparisons, although most of those exposures had a strong priori probability.
Towle et al. 2017[54]	16 case-control and 4 cohort studies, conducted in North America, Europe, and Asia. (1985-2016)	Ever-use of hair dye was associated with a non-statistically significant increased risk of leukemia (meta-RR 1.09, 95% CI: 0.97-1.22). Specifically, with permanent hair dye use RR = 1.19 (95% CI: 1.07-1.33), with dark hair dye use RR = 1.29 (95% CI: 1.11-1.50), with hair dye use among males RR = 1.42 (95% CI: 1.01-2.00), with hair dye use pre-1980 RR = 1.49 (95% CI: 1.21-1.83), and with hair dye use for longer than 15 years RR = 1.35 (95% CI: 1.13-1.62). When adjustment of smoking was conducted, ever-use of hair dye was not associated with leukemia, meta-RR = 0.99 (95% CI: 0.76–1.29).	The authors indicated exposure profiles that may influence the risk of disease were not adequately characterized (e.g., only collected information on "ever" use of hair dye) The authors further indicated the same control populations were applied in all calculations of risks for NHL, multiple myeloma, or leukemia; thus these calculations may not be considered independent; multiple comparisons may cause observed statistically significant associations that do not exist.
Qin et al. 2019[55]	13 case-control studies (10,399 cases and 20,013 controls) and 3 cohort studies (720,019 participants) (1988-2015)	The OR of 13 case-control studies was 1.13 (95% CI: 0.86-1.84), and the OR of 3 cohort studies was 1.16 (95% CI: 0.91-1.69). When all studies were combined, the random-effect OR = 1.14 (95% CI: 1.01-1.29). The OR of NHL was 1.38 (95% CI: 1.01-2.20) for female hair colorant users, while OR = 1.04 (95% CI: 0.86-1.25) in male users. The duration of hair colorant use recorded in these studies was divided into 3 groups: <10 years (OR 1.19, 95% CI: 0.90-1.88), 10-20 years (OR 1.20, 95% CI: 1.02-1.95), and >20 years (OR 1.34, 95% CI: 1.04-1.92). Regarding regional differences in these 16 studies, there were no prominent differences of OR values between North America, Europe and Asia.	Study objects in the present study were only from articles published in English or Chinese. Overall heterogeneity index I^2 = 79.7%, indicating that there was heterogeneity among these diverse studies. As the authors stated, across studies in the meta-analysis, various questionnaires were specifically designed for hair colorants; differences in color and coloring time of hair colorants may have resulted in the evaluation to be incorrect; telephone or E-mail follow-ups for hair colorant use were also provided with bias. The authors indicated bias may exist in consideration of the small quantities of some of the subgroup analysis data. Methodological discrepancies and confounding factors might affect the final outcome.

Table 3. Meta-analysis studies considered by the Panel			
Author	**Study involved (Published period)**	**Results**	**Note**
Odutola et al. 2020[56]	4 case-control studies and 1 pooled case-control study (4687 cases and 30,137 controls). (1976-2009)	Hair dye use before 1980 was positively associated with FL risk (meta-RR 1.66; 95% CI: 1.22-2.25; I^2 = 54.7%) but no evidence of effect after 1980.	Only articles published in English were included, and the identified study populations were predominantly Caucasian. The observed heterogeneity between studies examining smoking and former alcohol intake indicates low confidence in the validity of their respective meta-estimates. One pooled case-control study was included in this meta-analysis, which referred to Linet et al 2014[62], as summarized above.
Ahmadi et al. 2022[57]	28 case-control studies (12,313 cases and 27,955 controls) conducted in the USA, Europe, and Asia. (1990-2017)	In 17 studies, the pooled OR of hematopoietic cancers for general use of any type of hair dyes in women was 1.10 (95% CI: 1.01-1.20, I^2 = 58.2%). 11 studies investigated hair dye manufactured before and after 1980 as a risk factor for cancer; the pooled OR was 1.31 (95% CI: 1.08 - 1.59, I^2 = 59.5%) for using hair dye made before 1980, while the use of hair dye made after 1980 was not associated with cancer incidence (OR = 0.99; 95% CI: 0.89-1.10, I^2 = 1.9%). 13 studies examined the use of light and dark hair dye; the use of dark hair dye was associated with increased cancer rates (OR = 1.09; 95% CI: 0.95-1.25, I^2 = 47.8%).	The I^2 heterogeneity index for all studies on hematological cancers was 30.8%. The majority of the studies included were conducted among Caucasians. The inclusion criteria of the meta-analysis were case-control studies evaluating the association between hair dye use and cancer in women. As the authors discussed, the type of the studies included was all case-control, which was subjected to inherent problems such as selection bias as well as recall and observer bias (e.g., if the cases were more likely to report hair dye exposure, the actual effect might be misestimated).
Bladder Cancer			
Takkouche et al 2005[24]	The 9 case-control studies (5740 cases and 9290 controls), and 1 cohort study with 336 cases (547,571 participants). (1977-2004)	The pooled RR for all studies did not show any effect of hair dye on bladder cancer (RR 1.01, 95% CI: 0.89-1.14). After adjustment of smoking, the pooled RR = 1.05 (95% CI: 0.93-1.19). No substantial heterogeneity across all studies was detected (p = 0.41 in Q test). In the stratified analysis, RR = 1.13 (95% CI: 0.93-1.38) for permanent dyes use, RR = 1.33 (95% CI: 0.69-2.56) for intensive exposure (≥200 times), RR = 1.03 (95% CI: 0.90-1.17) for women and RR = 0.93 (95% CI: 0.77-1.13) for men.	As the authors pointed out, individual studies may have failed to control for potential confounders/effect modifiers; for instance, there were studies showing that bladder cancer among hair dye users is restricted to the specific genotype/phenotype of N-acetyltransferase, while such genetic factor as a potential effect modifier was not addressed in the individual studies.
Turati et al 2014[62]	15 case-control studies (8504 cases/deaths and 14,102 controls) and 2 cohort studies (617,937 participants). (1968-2011)	The pooled RR of bladder cancer incidence/mortality was 0.93 (95% CI: 0.83-1.05, I^2 = 34.1%) for personal use of any type of hair dye. When the subjects were stratified by sex: RR = 0.95 (95% CI: 0.85-1.06) for women and RR = 0.81 (95% CI: 0.64-1.02) for men. The RR for personal use of permanent hair dyes based on results of 7 studies was 0.92 (95% CI: 0.77-1.09). The pooled RR for the use of dark-color hair dyes was 1.29 (95% CI: 0.98 - 1.71), based on 4 studies reporting results for use of dark-colored dyes. No association was found between bladder cancer and the duration or lifetime frequency of use of any type of hair dye or use of permanent hair dyes.	The authors indicated that recall bias might exist for case-control studies, which represent the majority of studies included in this meta-analysis. The original studies may have failed to control for potential confounders. When considering 12 studies adjusting for smoking (the major risk factor for bladder cancer), similar results were obtained (RR = 0.94, 95% CI: 0.82-1.08).

Table 3. Meta-analysis studies considered by the Panel			
Author	**Study involved (Published period)**	**Results**	**Note**
		Brain Cancer	
Shao et al 2005[64]	4 case-control (1187 cases and 1321 controls) and 2 cohort studies (617,922 participants with 652 cases). (1986-2009)	No significant associations were found among the studies that evaluated permanent hair dye use and duration of any hair dye use. Pooled RRs of all studies for ever-use of any hair dyes were 1.13 (95% CI: 0.89 -1.45), 1.29 (95% CI: 0.94 - 1.78) for case-control studies, and 0.90 (95% CI: 0.78 - 1.05) for cohort studies. Similar results were obtained when the subjects were stratified by geographic regions (RR = 1.01; 95% CI: 0.80-1.28 for studies conducted in the USA) and sex (RR = 1.03 (95% CI: 0.80-1.33) and RR = 0.90 (95% CI: 0.60-1.50) for women and men, respectively).	All studies included in this meta-analysis were published in English. The authors pointed out individual studies did not adjust for potential risk factors in a consistent way while risk estimates were derived from multivariable models, thus the combined estimation might not provide clear results.
		Skin Cancer	
Takkouche et al 2005[24]	2 case-control studies (981 cases and 1427 controls). (1983-1988)	The pooled RR = 0.74 (95% CI: 0.51-1.07) for hair dye users vs. never users. For permanent dye use, in the individual studies, RRs were 1.1 (95% CI:0.8-1.6) and 0.6 (95% CI:0.4-1.0).	Only two studies were included in the meta-analysis.
		Ovarian Cancer	
Takkouche et al 2005[24]	2 case-control studies (247 cases and 316 controls). (1981-1993)	The pooled RR = 1.71 (95% CI: 1.15-2.53) for hair dye users vs. never users. Specifically, in one study, the RR = 0.91 (95% CI: 0.36-2.31) for the hair dye ever-use; in the other study, RR = 1.96 (95% CI:1.27-3.03).	Only two studies were included in the meta-analysis.
		Cervical Cancer	
Takkouche et al 2005[24]	1 case-control study (38 cases and 76 controls) and 1 cohort study (573,369 participants). (1981-1994)	The pooled RR = 0.89 (95% CI: 0.53-1.90) for hair dye users vs. never users. Specifically, in the case-control study, the RR = 0.70 (95% CI: 0.30-1.90) for any type of hair dye use; in the cohort study, RR = 0.97 (95% CI: 0.53-1.77) for hair dye ever-use, and RR = 1.51 (95% CI: 0.63-3.59) for intensive exposure (≥200 times).	Only two studies were included in the meta-analysis.

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APRIL 2017 PANEL MEETING

Dr. Marks Team – April 10, 2017

DR. MARKS: Now we'll go back to hair dye. Something that Ivan and I are very interested in. Do you want any, you made, some, a few comments, changes in red. A lot of it has to do with obviously cancer, and after you make your comment, Ivan, I'd like obviously Tom to react and then anybody else. Ron and Ron. So, Ivan, do you want to bring us up to date on that? And that's administrative page 35.

DR. BOYER: So, for hair dye, we've been monitoring the literature, looking for papers that might be relevant for updating this particular document, which we have posted online, which we refer to through a link that's incorporated into our safety assessment reports when it's appropriate. And it's been a while since we've updated anything. A few papers have shown up in the literature that seem to be relatively inconsequential, as far as the bottom line is concerned for this particular document. But we thought that, at this point, it'd be a good time to go ahead and incorporate those few papers that we have in this particular revision. And I guess to get the panel's feedback on whether or not simply accepting those changes is adequate, or if you see anything in there that might warrant some additional attention at this point.

DR. SHANK: I think you've done a great job. I don't have any change.

DR. SLAGA: I completely agree.

DR. MARKS: Okay. Sounds like we endorse the changes, Ivan…

DR. HILL: Yeah, I just had a couple of questions. When you mention, it's reference 15, it's the Chang et al, in cancer case control. Would it be appropriate to add any short sentence fragment on the nature of the association? When it says there's an association between this, that or the other, is there anything that can be? Do you know where I'm talking about here, it's exactly where the, search on associations. I usually highlight this sort of thing.

DR. SHANK: Is it page 41? On that table?

DR. HILL: Yes. I think that's it. That's exactly it. It's in the table where it's mentioned. I think that's the same reference where they re-analyzed what appeared to be the same data set. So it was more than 2007, is that the one? I'm not sure. Hold on. Yeah. John 2009 versus Morton 2007. I think it's the same data. Or that might be a different one. No that's a different one. That's a different one.

DR. BOYER: So, when you're asking for additional information on what the nature of the association, do you mean, for instance, the odds ratio that they may have calculated?

DR. HILL: It says an association between ever/never use of hair dyes, and the negative NHL was reported. That doesn't tell me anything. Just there was an association.

DR. BOYER: All of these studies have been summarized in a little bit more detail in the text of the document.

DR. HILL: Yeah

DR. BOYER: We try to keep it fairly short, and consistent as far as the information that we presented for each of the studies summarized. But I can take another look at it. The nature of the association is, at this point, you know, we've got these two different varieties of lymphomas. And one of them, there was a statistically-significant association that's probably represented by an odds ratio. None of the odds ratios exceed about two or so. So they're fairly small, and given the confounding factors typical in those types of studies, they're…

DR. HILL: I had been looking for something simpler, which was, it increased the odds of the cancer, or it decreased.

DR. BOYER: Oh, I see what you mean.

DR. HILL: Maybe that's implicitly obvious. That's so obvious, it couldn't have been that. It must have been a little more description but in there…

DR. BOYER: Okay

DR. HILL: But it sounds like there is no short encapsulation. From what you're saying. Sorry, I interrupted you. Didn't mean to…

DR. BOYER: That's fine. I'll take another look at it and see if we can include something a little more informative, without going into great detail.

DR. HILL: And similarly, just to enlighten, again, the reader can go out, but they have to go out and look at references, what the nature of the STAR 10 mutant of that N-acetyl transferase type one is the NAT 10. What exactly is the STAR 10? I actually had difficulty finding. But I think it's out there, I just didn't follow-up and finish before I got here. I was looking at this like two weeks ago. It was on my punch list, but I didn't get that far.

DR. BOYER: Mm hmm. Okay. I'll do that.

DR. MARKS: Okay. Any other comments about the hair dye boilerplate?

DR. BERGFELD: Was that to be an edit? And then it will go up on the website? Was that to be an edit?

DR. MARKS: Yeah. I think we'll have a discussion tomorrow.

DR. BERGFELD: Okay

DR. MARKS: And Ron Hill, you can bring it up. It sounds like Ivan, you'll take a look at it and see how it can be changed a little bit. But I didn't get a sense from Tom or Ron Shank that there was concern about this.

DR. SLAGA: My only comment about that would be, it's so weak, that you have to be careful how you state it. I mean you don't want it to come across like you're increasing cancer.

DR. HILL: Point well taken.

DR. SLAGA: So, the words, I like the way you have it.

DR. HILL: Okay. I mean, that's fine.

DR. MARKS: Okay. That's important, Tom. So it sounds like, Tom, as our cancer expert, would say leave it the way it is. Don't worry about smithing it. And we'll see what the Belsito team says tomorrow. Am I interpreting correct, Tom? Is that okay with you, Ron Hill?

DR. HILL: Yes. I still think a short description of what NAT 10 is belongs in there. And the STAR 10 allele. And also, similarly you've got arylamine acetyltransferases that can function to activate or de-activate arylamines. I've never encountered an instance of activating by acetyltransferases acetylation. And Ron Shank might have a thought on this, but acetylation, as far as I've seen, is always inactivating in terms of abolishing toxicity. So that's why you look at fast acetylaters versus slow acetylaters. In terms of certain drugs that have aniline-type nitrogens, or can have aniline-type nitrogens generated. That the acetylation, which is what the acetyltranferase is catalyzed, invariably deactivating.

DR. BOYER: So it sounds like what you're suggesting are basically some clarifications that wouldn't take much in terms of editing.

DR. HILL: No, in that particular case it's just function to activate or deactivate. I was sort of suggesting that we don't need activate, just deactivate. But I wanted to see if any of the others were aware of any cases where they saw that acetylation serve to activate. I've never encountered such.

DR. MARKS: I assume from a procedural point of view the Council, the Scientific Committee, will have some comments. And we're going to look at these documents again. Boilerplates with that in light.

DR. EISENMANN: Right, and this one is the Hair Color and Technical Committee that will look at it.

DR. MARKS: We'll have another look at this before it gets posted, I suspect. Unless that committee says everything looks fine and we can proceed.

DR. GILL: We were hoping to have a presentation at the June meeting from someone from that technical committee.

DR. MARKS: Okay.

DR. GILL: We've just decided to get this out earlier to get the thinking going.

DR. SADRIEH: I just have a question. So, I just want to understand that an increase in the arteries show two is not to be considered an increase in cancer? Is that what you're concluding? That an increase is not…

DR. SHANK: Statistically, it comes out so weakly, that most people I know consider it not to be a positive effect. It's a weak association is the only way I can describe it. It doesn't make it, I think if you use the word increase, it sounds like it's really increasing. That is questionable.

DR. SADRIEH: Okay. From one to two is not an increase. Is that? I mean, like a three would be an increase? What would be an increase then?

DR. SHANK: The change is insignificant.

DR. BOYER: You also want to look at the confidence interval. I mean if you have a two, and you have a confidence interval that doesn't include one, or the minimum is not far from one, then you would consider that to be a very weak association. On the other hand, if you have an odds ratio of 10, 11, 12 and so forth, and an odds ratio that does not include one, that exceeds one proportionally, then that would be a clear indication that there's an association. Generally, that's how epidemiological studies are interpreted. And there's good reason for that. There's a good argument that can be made to support that perspective, that way of interpreting those kinds of studies.

DR. MARKS: Thank you. That was helpful. Refreshed my memory on statistics 101. Any other comments on hair dye boilerplate? If not, then, tomorrow I'm just gonna mention that the format, the changes are fine with our team.

Dr. Belsito Team – April 10, 2017

DR. BELSITO: Hair dye. What page, and this is in admin.

DR. LIEBLER: 36.

DR. BELSITO: So with the bladder cancer, I mean again there's so much with these epi studies. There was that women who were college grads were more likely among hair dye users to have bladder cancer. I mean when you broke them out. And, again, were these studies controlled for smoking and other contributing factors, do we know? In this study by Ross, et al, 2012, a population based study -- Oh, no that wasn't the one. It was the one in New Hampshire, Vermont, right? Yeah. So in the Koutros 2011 study, the

study in Maine, Vermont, New Hampshire, the finding was an increase in bladder cancer with permanent hair dye use in a sub group of women with a college degree. But not dose response for color duration of use, or total lifetime uses.

And then the NAT2 phenotype was associated with a suggestive but not statistically-significant increase when college degreed women were stratified by education.

I mean I just point that out because, looking back at my childhood in the 50s and 60s, the mothers who went to college seemed more likely to be smokers, at that point in time, than the women who did not go to college in the 40s, because they were cool, educated, college women and sophisticated, and smoking was sophisticated. So, I mean, we know smoking is a risk for bladder cancer. So, in a lot of these epi studies, it just would be nice to get a sense of how well these were controlled. And then you have that whole issue of hair dye use pre 1980, post 1980, in terms of cancers.

Because there's no consistent trend, but then the data is also, it's the same with breast cancer. The Finnish study, there was an increase in odds of breast cancer in women who ever used hair dye, compared to those who never used hair dye. And it's a significant trend in the odds ratio for cumulative use of hair dyes. And that's coming out of Finland, where I would presume most women aren't using the same color hair dyes that the Italian women would be using. They're going to be much lighter colored hair dyes, if not blondish hair dyes.

It would be nice to see, and to report when we're doing this, whether they analyzed for other confounding factors between the control groups. What was the difference in bladder cancer among those who never used a hair dye? Did they smoke or not smoke? Did they even look at that? I mean otherwise I thought it was fine. I have no comments. We can continue to use it with the updates, but it's just that as I read through it, the idea of any confounding factors that might affect these cancers was never even mentioned.

DR. BOYER: It is pretty much standard practice for people who do epidemiological studies to at least do some sort of an analysis for the confounding variables. But they usually lump them together, so it's unlikely that smoking would be isolated as a single confounding factor in any one of these studies. But we can certainly bring forward --

DR. BELSITO: Just a brief statement as to whether confounding factors were looked at at all. They usually are, but not always.

DR. LIEBLER: I'm assuming these little paragraphs are mostly taking from the abstract from the papers.

DR. BOYER: No, actually they are our own.

DR. LIEBLER: I don't mean literally word for word, but you're distilling this from the main conclusions from the abstracts?

DR. BOYER: At least for the ones that I summarized, I've looked at the whole paper. And we rated the quality of the paper, let's put those plusses, double plusses, triple plusses.

DR. BELSITO: Right, four plusses.

DR. LIEBLER: The confounders are usually not mentioned in the abstract. But usually they are discussed in the discussion. And I'm sure you've looked at that. So that's there if you want it.

I took a very different approach to this document, maybe it was because I was near the end of my preparation, but I basically started with okay, for hair dyes, we basically take the position right now that there are no convincing data that support the causative relationship between hair dyes and cancers. So I'm looking at the new changes to see if any of those changed that conclusion. My assessment no. So we can update it, but doesn't change the conclusion.

DR. BELSITO: Yeah, fine. And I guess my point was a mention when we update it that confounding factors were or were not looked at in the report.

DR. SYNDER: Was that considered in your scoring scale, a one plus, two plus, three plus, whether they looked at confounding?

DR. BOYER: Whether they looked at confounding, no.

DR. SYNDER: Probably should. I have kind of a silly comment, but in the intro or something you should identify bladder cancer as urinary bladder cancer, not gall bladder cancer or something else.

Full Panel – April 11, 2017

DR. MARKS: The next is a draft update of the expert panel hair dye epidemiology. Findings and --. There are actually a number of changes in there. But our panel did like this also. So we'll mimic the Belsito team, at least in the previous drafts. We liked it.

DR. BERGFELD: Yeah. Belsito team. You liked it too?

DR. BELSITO: Yeah. I'm just trying to find out exactly where it is. Looking through dye and hair dye.

DR. MARKS: It's in page 35 in the Administrative tab there.

DR. BELSITO: Okay.

DR. MARKS: (inaudible)

DR. BELSITO: So, just off the top of my head, before I get to page 35. The one issue I had is, you know, yeah, the data is inconsistent. We say how we're looking at the data, yada yada yada. But, you know, there are some data coming out that are showing

some linkages. So, for instance, in terms of, I believe it was bladder cancer in women in New Hampshire and Vermont, if they were college grads, that incidence was positive, if they weren't it wasn't. And just, you know, looking back at my own childhood in the 1950's and my parents. You know, my impression was that women who went to college smoked a lot more than women who didn't go to college in the 1950's. And I was just wondering how well these studies are controlled for other confounders that could influence the cancer's in question? And in our boilerplate, we never mention that. So, I mean, they are epi studies. They are very hard to control. But did they look at other confounding factors that might contribute to these cancers? And so I'm fine with the document. I don't think that, in consumers, there's any strong evidence to suggest carcinogenicity of these hair dyes. I would just like, as we're going through the documents, a simple statement as to how well they looked at potential confounders in these studies that might contribute to the specific cancer endpoints in question. You know, like, for instance, even the relationship between cosmetologists and bladder cancer, you know, there are studies that show that cosmetologists smoke more than the general population. And then we know smoking is a risk for bladder cancer. So is it the hair dyes? Is it the other chemicals they use? Is it the smoking? Is it the combination of all of these? So, just a mention as to how well these studies were controlled for other confounders.

DR. BERGFELD: I'd like to make a comment. If you look at the references there, the references are in really strongly peer-reviewed journals.

DR. BELSITO: I understand.

DR. BERGFELD: I would think that those risk assessments, additional risk assessments, would have been made.

DR. BELSITO: Yeah. I mean, I think there should be --

DR. BERGFELD: A clarification would be well, but --

DR. BELSITO: -- at least a comment.

DR. BERGFELD: New England Journal, cancer. I mean, these are major.

DR. BELSITO: I'm not saying that they weren't.

DR. SLAGA: There's a lot of confounding issues and a good study that is peer reviewed, you know, that's one of the things they really look at. Are -- everything controlled for?

DR. BELSITO: Right. I understand. But we don't mention that in our --

DR. SLAGA: Yeah.

DR. BELSITO: -- reports. And I think just a one or two sentence mention that the following confounders were looked at.

DR. SLAGA: Yeah.

DR. LIEBLER: So, I think, even in the very best journals, the epidemiology is sometimes necessarily complicated by confounders. They can't be fully teased out and excluded, but need to be acknowledged, and are treated in their discussions.

DR. SLAGA: Right.

DR. LIEBLER: And this is going to be a case-by-case basis, where you might need to pull out something that appears interesting and potentially relevant from these discussions. And, Ivan indicated that he reviews the entire papers in preparing these. But I think it would be a good idea to consider, you know, looking at these carefully to see if there are any issues that were raised in a particular study that they said, you know, as possible confounder, we couldn't really resolve it. We think our conclusions are reasonably strong. But, and put the but in there for us.

DR. SLAGA: Right.

DR. BERGFELD: Good idea. I think that's a good editorial idea. Yeah. All right. Any further discussion. We have a next one?

JUNE 2018 PANEL MEETING

Dr. Belsito Team – June 4, 2018

DR. BELSITO: Hair dye epidemiology, I guess that’s the next one. That’s also in admin, correct?

DR. HELDRETH: That’s a separate book.

DR. BELSITO: Okay. Yes. I thought it looked fine. I had a couple of comments on PDF Page 3. The second line, third line -- so, let me see. It says, an odds ratio of 1 means that an exposure does not affect the odds of an outcome. RR of 1 means that there is no difference. I presume it’s an odds ratio of less than 1. There is a less than sign missing there? Third line from the bottom, PDF Page 3.

DR. LIEBLER: I think odds ratio don’t have a sign.

DR. BELSITO: Well, he’s defining what it means. And odds ratio of less than 1, I believe, means an exposure does not affect; and of 1 means there’s no difference; greater than 1 means the exposure my increase. He’s defining what odds ratios mean. Read the sentence. So, I think it’s an odds ratio of less than one means that an exposure does not. The 1 means there’s no difference; and greater than 1 means it increases the risk. So, that needs to be changed.

And then on PDF, Page 9, the first paragraph. The sentence of the first paragraph, the one, two, three, four, five, staring with, "Using a random effect model and the Duval and Tweedie's trim and fill procedure to adjust for publication bias in the presence of between studies heterogeneity." What does that mean?

DR. HELDRETH: I'm sorry, I was looking at another page. Where is that?

DR. BELSITO: PDF Page 9. The one, two, three, four, five, six -- six lines from the top, starting with using a random effects model. Are you with me?

DR. HELDRETH: Yes.

DR. BELSITO: Okay. Show procedure to adjust for publication bias in the presence of between studies heterogeneity. For publication bias for study heterogeneity? I don't understand what you're saying there.

DR. ZHU: That's the method they used in this paper, by this author, to do the meta-analysis.

DR. BELSITO: I understand the method, but the sentence makes zero sense to me. "For publication bias in the presence of between." Publication bias between studies? Publication bias because of heterogeneity of studies?

DR. ZHU: Okay. I think this method is used to evaluate the study's heterogeneity for different studies, epidemiology studies.

DR. HELDRETH: Right. But he's asking you -- the verbiage that's there isn't quite clear. Could you give us a better sentence?

DR. BELSITO: I guess my question is, what does the Duval and Tweedie's trim and fill procedure adjust publication bias for? For study heterogeneity? And then it says, "such meta-analysis showed." What is the bias that it adjusts for? I don't under that.

DR. HELDRETH: When they did the review of multiple studies, they excluded some studies. They had a bias, a rationale for why they excluded those studies, and possibly maybe that they're rationale was questionable. But that's to be assessed by the experts here.

DR. BELSITO: Right. I got the understanding that the trim and fill means they cut out some studies. I understand that. But for publication bias. I mean, what is in the presence of between studies heterogeneity? Publication bias because there was a lot of heterogeneity between the studies they put in the meta-analysis?

I don't understand what they're electing to trim. That sentence makes no sense to me and doesn't explain to me what that model is.

DR. ZHU: Sure. This is a model used by the author to do the meta-analysis.

DR. BELSITO: I understand. What I'm saying is, please look at what the model does and put it into a better sentence that makes it understandable as to what it's doing.

DR. ZHU: Sure.

DR. BELSITO: I had no other comments.

DR. LIEBLER: I just wanted to return to the odds ratio sentence because I think it was correct as originally written. So, this is again the bottom of Page 3 on the PDF. If we're talking about the same sentence, Don, I want to make sure; an odds ratio of one means that exposure does not affect the odds?

And if it's 1, that's exactly correct. If there's a lower risk of the outcome as a function of exposure, then that's when the odds ratio is less than 1, like .8 or .6 or .5. But as written, it was correct, so, it doesn't need to be "less than" added to that sentence.

DR. KLAASSEN: Well, the other aspect of these odds ratio is that they always give a confidence -- or a range. So, you can have an odds ratio of 1.5, but if the confidence interval is 0.9 to 2.3, it's not significantly different. It's kind of an over simplification because it's the odds ratio with the 95 percent confidence interval. For it to be significant, you not only have to have the odds ratio, but the 95 percent confidence limits greater than 1.0.

And there's a lot of them that are 1.4 that are not significantly different because you have the 1.4, and then your confidence interval goes from 0.8 to 2.3. So, then that's not significantly increased. Just so everybody realizes that.

DR. HELDRETH: Okay. Should we then add a small section about confidence intervals?

DR. KLAASSEN: I think for people that aren't familiar with that, and some people that are reding this probably aren't.

DR. LIEBLER: I think as written, it does at least introduce what the odds ratio and relative risks are -- defines them clearly enough.

DR. KLAASSEN: Yes.

DR. LIEBLER: But then I agree with Curt's suggestion that perhaps we add a sentence or two at the end of the paragraph to explain that typically odds ratios are presented with calculated ranges based on the application of the appropriate statistical test.

DR. ZHU: Okay. Will do.

DR. BERGFELD: I was confused with just the tabulation of all these different studies. And the takeaway message is what? Is it presented here in the first couple of paragraphs, conclusion? I think it's in the first paragraph, in the beginning of the document. Because you end this document with the DNA repair enzyme genes and no summary, no discussion, no nothing.

DR. LIEBLER: You think we ought to move the conclusion paragraph to the end of the document?

DR. BERGFELD: I think like all of our documents -- this is a lot of information. Somewhere there has to be a summary in a few paragraphs, maybe, and a conclusion. I don't mind keeping the conclusion up front, but when I was reading this, I said, is this this conclusion, or is this the past conclusion? Because we've concluded the same thing in the past.

And then when it ends so abruptly. What is the information that we're passing on, risk, no risk? Maybe a risk?

DR. BELSITO: I agree with the conclusion part. I think the information is summarized under each of the cancer endpoints, prostate, bladder, breast, et cetera. And then at the end, you know, come to a little bit of a discussion that there have been reports of these various cancers associated with hair dyes. However, in reviewing all of the reports, there is no definite link between personal use and any of these cancers. And then our conclusion.

DR. BERGFELD: You agree that it should be added?

DR. BELSITO: Yeah. I mean, I see your point. I didn't see that when I was reading it because the conclusions were said, all at the end, for specific endpoints; but you're right. It could be taken that the conclusion up front was our prior conclusion and then at the end, we reviewed all of this and we haven't been able to make a conclusion. It's not the usual place that a conclusion is placed, at the beginning of a document.

DR. HELDRETH: For that conclusion that we're going to put at the end, is it the same verbiage that's already in the front? Or is there something different that the panel would like to say at the end?

DR. BELSITO: I think that the introduction should be what we had previously look at and what our prior conclusion was; and that since that time there had been a number of other reports, as outlined below, that have looked at these issues. And this is an update in our prior report, and a reconsideration of our conclusion.

DR. BERGFELD: With a date.

DR. BELSITO: With a date. And then go through all of this and then come back. And the conclusion can be the same; but it just points out that since 2014, or whenever it was that we last looked at this, we've now looked at all of the studies and still do not see a reason to change our initial conclusion.

DR. BERGFELD: Do you think there's a reason to put somewhere in the discussion that Dr. Naldi was asked to review these, that an expert reviewed it?

DR. BELSITO: I thought it was sort of clear there, but yeah, I mean, that's important.

DR. BERGFELD: I mean, it isn't just us looking at it, we've had an expert look at it.

DR. SNYDER: I agree with the Council's comment that we should change this to a guidance document.

DR. BERGFELD: Resource.

DR. SNYDER: Not from -- a guidance -- resource document from a guidance document. I think that the opening paragraph, which has been discussed here largely, should just be like one of our reports. It should be very succinct, like almost abstract form, and that language is exactly what we incorporate into the report.

And before that, we say this document was last updated, and give the date; just like we do in our regular reports with a thorough literature search and consideration. Any new publications relevant to the epidemiology of the association between hair dye use and various cancers.

But I think that the opening thing should be exactly what we take, and that should go straight into our reports for hair dyes. And under that we can give the methodologies that we use to generate this resource document. And then followed by all of the brief summaries of all the individual studies.

DR. BERGFELD: And then a discussion/conclusion; it's the same format?

DR. SNYDER: Yeah. I think almost like one of our reports. I think that would be the most succinct way to handle it.

DR. HELDRETH: Okay. So, then the suggestion is that we expand this from the type of document -- the hair dye epidemiology document that it was -- and make it also have a boilerplate functionality to it?

DR. SNYDER: That's the recommendation. Then you can clearly see where the language comes that we take from our resource document; and then it's updated, and then it goes into our reports as they're published, subsequent to the most recent update.

MR. GREMILLION: I have a clarifying question. So, the expert is only between hair dye and breast cancer; is this doctor Naldi a dermatologist?

DR. BELSITO: Dr. Naldi is an epidemiologist in Bergamo Italy. I know him through his work in dermatology. He's considered a real expert epidemiologist. He consults for the Research Institute for Fragrance Materials, and a large epidemiologic study that they're sponsoring in Europe called the EDEN Group. So, he may be associated with the Department of Dermatology, I don't know, but his background is as an epidemiologist.

MR. GREMILLION: I also wanted to call attention to kind of an inconsistency I saw in his report. At the end of this document he says, "The available evidence linking hair dye use and breast cancer is limited but warrants further investigations." And earlier in the document, just half of that sentence, "The available evidence linking hair dye use and breast cancer is limited" period, is stated. I just felt like that was maybe a little bit of a mischaracterization of what he concluded.

DR. HELDRETH: I think the intent of -- and you know, I'm just trying to understand it from reading it myself. But I think the intent there was to lay out, well there may be some epidemiology studies here that maybe there's some sort of association or maybe there's not. But either way, epidemiology studies never give you cause and effect. Even if it came out with a strong odds ratio, that still would not mean that there's cause and effect. And there would need to be further study done to see if it's an actual causality.

DR. BELSITO: I actually took that as being, okay, here's the opening remark. It's limited, here's the data. And after looking at this limited data, here's my conclusion. It starts, the available evidence linking hair dye use and breast cancer is limited. It is limited. That evidence is limited. He's reviewed the evidence and his conclusion is that further studies are warranted.

MR. GREMILLION: Yeah. And the conclusion that further studies are warranted is a reason that -- implicit in that is that there is some evidence out there that would make you want to look for more evidence.

DR. BELSITO: Usually, when you say further studies are warranted, in science, it's because there's no definite data. It's that the studies that exist are limited, they don't conclude one way or the other, and therefore, more information is needed.

DR. SNYDER: Because the effect could be a compounding effect and have nothing to do with hair dyes. And so, I think that's what he's alluding to.

MR. GREMILLION: Sure, but to say the available evidence is limited, but warrants further study, versus just, the available evidence is limited. I mean, the first says something about the body of evidence is out there but warrants further study; then there's some reason to believe that the further study may illuminate some relationship.

DR. BELSITO: Or just the opposite and show that there's no relationship.

DR. SADRIEH: I think maybe it would be a good idea to kind of suggest what kinds of studies would be needed. Because, you know, the types of studies that have been looked at is case-control studies, which basically come with recall bias. So, I think that there's going to be inherently -- you're never going to find an association, even if you find a good relative risk or odds ratio, or whatever.

The question is, what would be enough? I guess, from my perspective, the way that this is being evaluated and by not really doing a systematic review, I don't know really what this kind of analysis is going to end up reporting; because there is no way of being able to get any information that is going to be useful in anyway.

I would maybe suggest that we look into the possibility of the types of studies that would be useful. And if they are prospective study that has to be done, then how would they have to be done? And if it's a systematic review of the existing literature, then how would that have to be done, to then weight the studies such that we actually can draw conclusions that are useful?

Because right now it's just kind of look at the information, you know, the previous data that wasn't conclusive. This date is not conclusive, I doubt that any data is ever going to be conclusive if we keep looking at the information in this manner. Thank you.

DR. BELSITO: Bart, maybe we can get back to Luigi and ask him what kind of studies he would, as an epidemiologist, believe would answer this type of question. And then further studies, further prospective studies, further da-da-da kind of studies, would be needed.

DR. HELDRETH: We can certainly pose that question to him.

DR. BERGFELD: Is that in the purview of this panel?

DR. BELSITO: I think it's in the purview of the panel to try and determine the safety of hair dyes. Normally, we don't conduct studies, but we're having an epidemiologist look at this and saying that the studies that exist aren't adequate.

And we will oftentimes, in the purview of the panel, say we wanted 28-day dermal toxicity and if it absorbs in other toxicological endpoints. So, we're not specifying the study in detail, but getting a comment as to what kinds of studies might help address this situation.

DR. BERGFELD: Most of the data, though, I believe said in 1980 there's a change in the epidemiology looking at breast cancer. The earlier dyes may have been carcinogenic. The newer dyes --

DR. BELSITO: The big issue is the new data that suggests African American woman have a higher risk of breast cancer with hair dyes; which sort of raised, for a lot of people I think, the question, are darker colored hair dyes of greater risk in terms of breast cancer? And that's always been a question in regard to other types of cancers as well. I do think that needs to be addressed in some fashion.

DR. BERGFELD: And also, they have to define what hair dyes they're actually using. Some of them are old types.

DR. LIEBLER: We talked about the conclusion and how the report just sort of stopped at the end of the narrative of the data review. Sometimes, when you have a document like this, it helps the reader to have not just a conclusion, which is usually very brief and probably maybe overly general, to have maybe a couple of paragraph discussion that summarizes the outstanding issues and what are the issues that probably won't be resolved by further studies of the types that have already been done and the meta-analyses that have been done.

So, in other words, what are the -- anyways, Don just pointed out, the association with breast cancer risk in African American women with hair dyes. That seems like a significant, interesting issue that could be resolved by another focus study, possibly. But the broader question of hair dye association, we've got actually a lot of data. And it's basically very modest affects and the data are consistently inconsistent. In other words, there's a consistent marginal affect a little bit. Plus, a little bit, you know, higher than 1, a little bit less than 1.

But I think perhaps a paragraph that summarizes kind of what are the main outstanding questions that remain, and what issues are probably not going to be resolved any better than they're currently resolved, followed by a conclusion.

DR. SADRIEH: That may be true, but at some point, one has to address how one would resolve these questions. I think, you know, there has to be a way to be able to move sort of the answer a little bit forward, other than to say that, you know, there's no way that a link can be established because --

DR. LIEBLER: No, I wasn't saying that. I wasn't saying that. I think sometimes it's good to just step back and say, okay, what have we learned? What are the questions that we could resolve, and how could we resolve them? And what are the questions that we're unlikely to be able to resolve with these types of studies?

DR. SADRIEH: Right. But then we also have to say what kinds of studies would we have to do in order to -- so, identifying the deficiencies is one thing. But we have to also say, how are we going to address the deficiencies.

DR. HELDRETH: Isn't part of the answer to what kinds of studies would be done, it would be studies other than epidemiological studies, typical carcinogenicity endpoints that we would study where we were looking at a chemical and we're seeing an endpoint effect?

DR. EISENMANN: Hair dyes are very carefully studied for genotoxicity. And they've been coming up negative, the current hair dyes that are used.

DR. SADRIEH: Yeah, but you can't answer sort of the human risk aspect with the genotox or an animal carcinogenicity study. You have to look at human data. And I don't think you could do a human cancer study. So, you're going to have to look at epidemiology data and, you know, the studies have to be either prospectively designed -- I mean, I think a lot of the studies here are sort of other studies that were being done and they kind of asked an extra question about hair dye use, without knowing which hair dye, how often, what was the formulation, anything. So, you know, I think it's very difficult to draw conclusions from doing such a superficial review and then coming up with a conclusion that, you know, there's no evidence. Because I think that can be even more misleading than anything. Because you really haven't done the effort of trying to answer the question or identify what needs to get done to answer the question. And then the response is somewhat minimal and probably not helpful to the public.

DR. EISENMANN: One other comment that we have on our comments is back in 2006, Dr. Rollison did that paper and suggested the scoring of exposure for every epidemiology study. And that's been taken out of the table of this report. We'd like to see it put back in and, for the new studies, for that scoring to be added. So, it would be rated as to -- was the exposure just yes or no or was it more in detail about --

DR. BELSITO: So, you're talking about what is a Gemlish (phonetic) score? Is that what you're asking about?

DR. EISENMANN: No, it was Dr. Rollison score. It's in the text of some of it, and it used to be in the table, but it has been taken out. If they need the paper again, we can provide it. But she explained how to score exposure.

DR. ZHU: We have the paper, so I can add it back into the table.

DR. SADRIEH: Thank you.

DR. BELSITO: Any other comments on hair dye? Okay.

DR. BERGFELD: I have a comment. It would seem to me that this hair dye document needs to come back again for review comment.

MR. GREMILLION: Just kind of random observation. On Page 18 of the PDF, he says, "Taking skin cancer aside, breast cancer is the most common cancer diagnosed in women worldwide." And that's at odds with the World Cancer Research Fund International. They said lung cancer was the most common cancer; and skin cancer is down there, pretty far. There's just some odd --

DR. BERGFELD: Usually melanoma ranks about third or fourth.

DR. BELSITO: Yeah, but skin cancer is not just melanoma; it's basal cell and squamous, which aren't reported. So, he's correct. And this is speaking about women, not population in general. And I think it's men who skew lung cancer ahead of breast cancer. Any other comments? Okay. Polyaminopropyl Biguanide.

Dr. Marks Team - June 4, 2018

DR. MARKS: Oh, now we're into the hair dye epidemiology. That's going to be significant. Here we go, let's see. Where do I have that? Here it is. And I am not fluent; and I assume -- is this Chinese?

DR. ZHU: It's Jinqiu.

DR. MARKS: Jin --

DR. ZHU: Jinqiu.

DR. MARKS: Jinqiu.

DR. ANSELL: A new CIR writer.

DR. MARKS: Oh, I know that. I was getting the pronunciation of Jinqiu's first name. And the last name is Zhu?

DR. ZHU: Zhu.

DR. MARKS: Zhu. So, I could say Dr. Zhu. That actually is easier in some way. But at any rate, thanks for your memo dated May 23rd. We had the latest draft. Particularly, regarding breast cancer incidences and the evaluations from Dr. Naldi.

And one of my comments, I guess, I would make, right off the bat; and then I'll ask Ron, Ron and Tom, is Dr. Naldi -- if I recall correctly, he's the head of dermatology at Vicenza. Is that correct? University of Vicenza?

DR. ZHU: He's also an epidemiologist.

DR. MARKS: Yeah, okay. I figured that. Well, not figured, I assumed, that had to be, that he was being used as an expert in epidemiology. But probably some way that should be captured. Obviously, now it's captured in the minutes.

I expected that would be the case, but I was a little bit interested. A dermatologist, also an expert in epidemiology. Not excusive, obviously, but it's not very common in my experience.

DR. HELDRETH: Yeah. Dr. Belsito had recommended him because with his work in epidemiology, he's also helped the RIFM panel as well.

DR. MARKS: RIFM, okay. That makes sense. I didn't know that history. But at least now it's in the minutes. Comments on this? And then there was some -- was it this morning that we had -- yes, this morning we got a memo from Alexandra Kowcz. How do you pronounce her last name?

DR. HELDRETH: Kowcz. Yeah, Kowcz.

DR. MARKS: Codish. Huh?

DR. HELDRETH: Kowcz.

DR. MARKS: Kowcz.

DR. ANSELL: Like the company.

DR. MARKS: Okay.

DR. HILL: Put me in coach.

DR. MARKS: At any rate, there was some comments there dated June the 4TH, so we should note those. Key issues, additional considerations. First, do you want to make any comments, particularly, about -- Dr. Zhu, in reference to the comments from the industry liaison to Bart?

DR. ZHU: You mean my comment on the --

DR. MARKS: Yeah. Do you want to preface anything either --

DR. ZHU: Yeah, I agree.

DR. MARKS: Dr. Naldi and this memo here? You've had a little bit longer time to see it, not much, than we had.

DR. ZHU: Okay. I have the comment.

DR. MARKS: While you're looking at that --

DR. SHANK: Nothing to add.

DR. MARKS: Ron Shank, nothing to add, okay. You like it.

DR. SHANK: Yes.

DR. MARKS: Okay.

DR. SHANK: Very clear.

DR. MARKS: Tom?

DR. SLAGA: Same here. I didn't have no problem with it. Very clear.

DR. MARKS: Good. Okay. Did you look at the memo?

DR. SLAGA: I left mine in the other room, I think.

DR. MARKS: We'll take a minute and let -- Tom, for you to look at the memo. And I see that both Rons are reading over the memo also.

DR. WYATT: Is there an extra copy of the memo from Alexandra?

DR. MARKS: Pardon?

DR. WYATT: Is there an extra copy of the memo from Alexandra?

DR. MARKS: I just gave mine. A minute ago, I would have said, yes. But -- do you have an extra copy of the memo?

DR. ZHU: Yes. I have it.

DR. MARKS: Could you give me a copy or give this gentleman a copy.

DR. ZHU: A copy? I just have it on the computer.

DR. WYATT: My name is Mr. Wyatt; I'm with the FDA.

DR. MARKS: Okay.

DR. HILL: Should I go check out with Carla and see if there's one out there? An extra? There usually --

DR. MARKS: Well, if you've read it, maybe you could loan it.

DR. HILL: He's got an electronic, doesn't he? I thought that's what he was saying.

DR. HELDRETH: We don't have any extras. We got these this morning too.

DR. MARKS: Oh, you got it this morning too. Okay, so that is real time.

DR. WYATT: Understood, thank you.

DR. MARKS: Would Carla have it? Carla wouldn't have extras. I gave mine to Tom.

DR. ANSELL: Okay, we have one.

DR. MARKS: Do you want to look through it? Did you get to skim it or not?

DR. WYATT: I can just --

MS. FIUME: I know it. Yeah.

DR. MARKS: You know it.

DR. WYATT: I could just do the cursory look.

DR. HILL: Because it's not on the website yet, right? You got a phone, you could take a picture of it.

DR. MARKS: Again, Dr. Zhu was -- did you get to read the memo?

DR. ZHU: Yes.

DR. MARKS: Is there any comments the way you're going to change the boilerplate? I guess it's -- I'm not sure. I guess the boilerplate or at least an epidemiology update. Was there anything in the memo that you specifically --

DR. ZHU: The comment on the paper 2017, Dianatinasab paper; so, this comment indicated that the word, you know, risk should not be used. Instead use the association. Actually, the risk word, this word, risk, is used by the author in the paper. So, I just quote that.

But actually, I agree that we can use the word association instead of risk. Because, you know, in this paper there are multiple disparate factors has been compared. I think the -- because some of them shows a positive result; some of them shows a negative result. In our document, I agree that we use association instead of risk.

And I agree, you know, in the Table 1, we should correct that -- that should be prostate cancer instead of breast cancer. And also, I agree that in Dr. Naldi's write-up of the 2015 paper, because this here it indicated that when the odds ratio for more than 19 hair dye episodes used, that information has not been included in our Table 1. We should include that into our Table 1. Yeah.

And also, the comment on Dr. Naldi's write-up of the Mendelsohm 2019 paper; yes, I think Dr. Naldi just did not say clearly here, that -- but that should be corrected in our revised version about the three years use of the hair dye survey; that information can be updated. And several other things, you know --

DR. MARKS: Okay. Tom, any comments? You still like any -- and these changes suggested in the memo, they're fine?

DR. SHANK: Yeah. The editorial changes.

DR. SLAGA: Minor, yeah.

DR. MARKS: Yeah, they're fine. I think the bottom line is when I read -- and that's not yellow, but I want to be sure, Tom, Ron and Ron, you're fine with this. The conclusion is, the CIR expert panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer, based on the lack of strength of the associations and inconsistencies of the findings.

In addition, the panel noted there was no consistent pattern of genotype/phenotype influences on hair dye, epidemiology findings. These new studies all support, still, that conclusion.

DR. SLAGA: Yeah.

DR. MARKS: Okay. Because that's the bottom line for this. Okay, any other comments?

DR. SHANK: I don't see how they'll ever show an association between something like hair dye use and adverse health effect.

DR. SLAGA: Yeah, even if it's a specific --

DR. SHANK: You have to do individual -- they're not all the same.

DR. MARKS: Right.

DR. SHANK: And until you do a quantitative study, on particular dyes, you really have a very slim chance of coming up with a significant association. Not that there is or isn't one, it's just there's no power to the analysis.

DR. HELDRETH: I think that's probably what the casual reader wouldn't conclude. They would wonder, okay here's all these studies and we don't think it's a problem. But I think the explanation you just gave would be a great addition, I think, to the document. I think that would make it clearer.

But it's up to you whether or not we should make that kind of addition. Because I think there's a couple instances, throughout the document, where it says further study may be warranted. But as you mentioned, the study's probably not possible.

DR. SHANK: Right.

DR. SLAGA: You'd never have enough with one specific hair dye.

DR. SHANK: Would you be willing to put that kind of statement in the hair dye epidemiology -- what do we call this -- paper? It's up to us?

DR. HELDRETH: It's up to you.

DR. MARKS: Document. That's what the -- Jinqiu? Am I saying that correct?

DR. ZHU: Yes.

DR. MARKS: Jinqiu, that's what he has. Hair dye epidemiology document. So, it's a document.

DR. SHANK: Document.

DR. MARKS: So, it's already now in the minutes for public consumption. It's not a matter of -- the question is, do you think it should be explicitly put in this document? That's very interesting. And would that help guide future epidemiologists in terms of trying to really determine.

DR. SHANK: Well, doing more studies like this, even with genetic markers -- there's one that had interesting genetic markers -- is not going to give you the scientific power to identify which dye.

It's not hair dye use that's going to cause cancer; it's particular hair dye that could. And if you lump them all together, with no quantitation or very little quantitation --

DR. SLAGA: Well, you have the delusion effect of bringing them all together, too.

DR. ANSELL: I don't think we are directing research. I think -- and Linda's clearly the expert here, but I think our process has been to continue to monitor the research and to make it available to you guys. I think your point's well taken, but none of us are actually running a research program.

I don't know how we would even -- what we would do, just send it into the ether, saying we think this would be type of study --

DR. SHANK: We can dictate studies. Every time I read further studies are recommended, I kind of cringe. Because these are extremely expensive studies. Epidemiology is not cheap.

And if you start off, really, with a very poor chance of coming up with a meaningful association, it's money not well spent. But I don't think we can say that in our document.

DR. SLAGA: We can't dictate that.

DR. ANSELL: Nor would you suggest that we stop our monitoring and reporting?

DR. SLAGA: No. No.

DR. SHANK: We should continue to monitor; I did not mean that. But I don't like recommending more studies.

DR. ANSELL: Okay.

DR. MARKS: And I think that's an important point. Because if we recommend more studies, then we should give what we think the studies may be. If I understood what you said, Ron Shank, correctly. If we're going to identify any cancer potential, it needs to be for specific dyes, not in a general --

DR. ANSELL: But we don't say that, do we, in our summaries; that we recommend additional studies?

MS. LORETZ: Oh, no. No.

DR. ANSELL: Our roll, or what we've taken on as our responsibility, is to continually monitor the research as it's being done with all of its bumps and bruises. And just make the panel aware that -- I think there was a specific study, which Don wanted to have an expect look at, and he's provided his comments.

DR. SLAGA: Yeah. I mean, no and that's important in itself.

MS. LORETZ: So, this gets revised then? I mean, and then what happens next? Or is there another comment period? Or how does that work?

DR. HELDRETH: If there's going to be substantive changes to it. If it's something as simple as changing the verbiage or put the relevant study back in the table, where it was before, and nothing's really changing and the conclusion's not changing, the panel can say go ahead with those changes and it's fine. But if you want to add some verbiage that's a substantive change, then, sure, we would want to put it out there for public comment again.

DR. MARKS: I think, addressing Ron, we do say if we use this document as such. If you look on page 9, just as Ron said, it's in the yellow highlighting right above genetic polymorphism.

The last sentence. "While these findings do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted." And that's exactly what Ron is talking about.

I think, Ron, the question is, do we want to keep that sentence or eliminate that one. Because that's exactly what you were talking about.

DR. SHANK: It's almost the standard statement, more research is needed. Every scientist says that because --

DR. MARKS: That's how they keep busy.

DR. SLAGA: That's how you get money.

DR. SHANK: I had to stop midsentence on that.

DR. MARKS: Yeah, I know. But I'll finish it.

DR. SLAGA: I don't want Ron on my review committee if I submit an epidemiological study on hair dyes.

DR. HILL: Well, but it is a policy question, and this is something off -- it's on the record, but it's off the record. Is do you spend a lot of money on an epidemiology study; or is it better to go at it from the other direction. Okay, we have this mechanism, is there any connection to a dye that's being used, potentially.

You know, and to me, you spend the money on the biology, in general, keep the epidemiology cooking maybe; but the only one that I ever saw even a whiff was for about 10,000 professional hair dressers in China. And there wasn't still not statistical power, but a whiff of something that makes some sense. And that was the best I've seen in all of it.

DR. MARKS: So again, just to continue beating this horse, on Page 5, right above lymphoma and leukemia, again, while Tai et al. findings are limited and do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted.

We're back with ending a lot of these by saying, well it didn't show anything, but do more investigations. I shouldn't say it didn't show anything, it didn't support a causal relationship. Do we want to just eliminate those parts of this document that says further investigation? We know they're going to be further investigation.

DR. SLAGA: It's followed by maybe, so it's okay.

DR. MARKS: Yeah, maybe.

DR. SHANK: It doesn't say epidemiological investigations. But keep looking for --

DR. MARKS: Further investigations. Yeah, that's true.

DR. SHANK: Keep looking for any risk.

DR. MARKS: Okay. No, I think --

DR. ANSELL: I also think there's a difference between reporting that the author has concluded versus the panel recommends.

DR. MARKS: Right.

DR. ANSELL: And so, this is, well his finding are limited, so who is saying additional data here?

DR. HELDRETH: We are. That was the verbiage -- we were following up with what Dr. Naldi was saying. And so, we characterized it in the way that he had. And he makes those kinds of statements throughout, further should be done.

DR. ANSELL: So, I think we could change that.

DR. MARKS: Well, I don't know that we need to change it, because I think Ron's comment that when you say further investigation, that leave it wide open, not necessarily epidemiologic investigation.

DR. SHANK: That's right.

DR. MARKS: I think I like the way you interpret that. I think leaving it in, from my mind is fine. If that's okay with Ron, Tom and Ron.

DR. SHANK: It is with me.

DR. HILL: It is me, too; because I think investigation means if there really is -- I mean, you make the hypothesis there really is something and then try to figure out if there's mechanism. And of all the things society spends money on, to me, science should be more and other things less. There's never enough science.

DR. MARKS: Okay. We're going to be seconding, probably, I would think, a proposal to post this revised draft hair dye epidemiology document on the website. And we like the way it is, and our minutes will capture the nuances about doing epidemiologic studies on specific dyes, not general dye exposure. And that further investigations covers the waterfront.

DR. HILL: We did see something interesting from a presenter -- not the last meeting, but I think the meeting before -- that looked at differences between light colored hair dyes, certain exposures, versus dark ones. I thought that was an example of, that's interesting now let's see what that means.

DR. MARKS: Okay. Any further comments? Thank you Jinqiu. The J is like a Z? Jinqiu.

DR. ZHU: Yes.

DR. MARKS: Good. You're going to educate me. I apologize for my ignorance.

DR. HELDRETH: He's also told us in house that we can call him James. So, if that's easier.

DR. MARKS: James.

DR. SLAGA: What was that? I didn't hear.

DR. HELDRETH: Oh, he also told us in house, instead, we can just call him James if we want to.

DR. SLAGA: James?

DR. HELDRETH: Yes.

DR. MARKS: I may revert to that in the next meeting if I can't remember. I mean it's just knowing how to -- the J is a Z. Jinqiu.

DR. ZHU: Jinqiu.

DR. MARKS: Jinqiu. Okay. Thank you for tolerating us. Okay, we've got a little less than 15 minutes to go to lunch. We can do the next one. This is straight forward, right?

DR. SHANK: Sure.

DR. MARKS: Yeah, sure is right. Well, it's only one ingredient, correct?

DR. SHANK: Yeah.

Full Panel - June 5, 2018

DR. BELSITO: First of all, we liked the council's suggestion that these boilerplates be referred to as resource documents, going into the future; we like that terminology. In terms of the hair dye resources document, Dr. Naldi did some analysis, particularly on the new information that had come in regarding associations between hair dye use and breast cancer, particularly in African American women, and we appreciate that very much.

There were two additional studies that were available, subsequent to his analysis, that we would request that he relook at. And there was also concern, particularly from the Consumer Federation of America, with his last sentence that says, "While these findings do not represent evidence for the presence of a cause-effect relationship, further investigations may be warranted." And, therefore, I think a request should go back to Dr. Naldi as to clarifying that statement and what kind of investigations would be needed to try and resolve this question.

DR. BERGFELD: I'm sorry to interject, but being in your team meeting yesterday, was there also a suggestion of reformatting this document?

DR. BELSITO: Yes, that has to do with reformatting; the fact that the conclusion is stated up front rather than at the end and having -- we agreed that there can be discussion at each endpoint in terms of the cancers looked at, as to our assessment of the data that has been presented in terms of whether there is risk or not. But then at the end of the document there should be a final conclusion rendered, rather than the conclusion up front.

DR. BERGFELD: Thank you. Any comments. Dr. Marks?

DR. MARKS: Yeah, Ron Shank, I think had a pithy comment yesterday. Rather than me try and paraphrase it, Ron was referring to the epidemiologic studies as I understand. And as long as they're done with multiple dye exposures, it's hard to come to a conclusion. That really needs to be with a specific dye.

And that, actually, we thought that further investigations was not a bad -- maybe clarify it -- but how we interpreted that is it covers all science and all toxicity. So, as we get more mechanistically driven, those would be the studies that probably would help us move forward. But Ron, please clarify what I think I heard you say.

DR. SHANK: You said it right. I think when you do epidemiological studies, such as been done in the past, where you're having a very broad sweep of the cost of agent, hair dyes, that's way to general to give any power to the epidemiological study, to come up with an association. And future studies should focus on particular hair dye. And there're many of them so this is probably going to be very difficult to achieve. So, when we say more studies should be done, I think what we mean, more studies but not just epidemiological studies.

Basically, that was it; that I thought the CIR panel should continue to monitor new information that comes out. But I don't think we should say there should more epidemiological studies, in particular, more investigations.

DR. SNYDER: Can we use language along the effect that these are largely observations, and that the cause and effect remains to be determined? Something along that line, rather than specify studies. We just say that the cause and effect remains to be determined.

DR. SHANK: Yes. Thank you.

DR. BERGFELD: There was some suggestion yesterday that we -- in the formatting of this particular resource document and perhaps the innovation one as well, in some other white hat kinds of statements that we've made -- that we put them together similar to how we put our ingredients reports together. With an abstract, what's been considered, and then the fill-in parts, as well as then a discussion and a conclusion. And I think that would be a better reading document.

Because this one left me particularly cold; what else is new kind of thing. All right. Well I think that we'll move forward with that. We don't need to have any vote on that, do we?

DR. HELDRETH: I don't believe so.

DR. BERGFELD: No, I don't think so.

DR. HELDRETH: Going forward Jinqiu will go through and make these sorts of edits, and reformat the document, and then it will come back to the panel again for finalization.

DR. BERGFELD: I think that you were going to also contact Dr. Naldi, and request what from him?

DR. HELDRETH: From Dr. Neldi we'll be requesting his outlook on what is meant by further investigations; and to have him look at the two studies that were discovered after he did his analysis.

DECEMBER 2018 PANEL MEETING

Dr. Marks Team – December 3, 2018

MS. FIUME: Okay, so the next two require Jinqiu's input because he prepared these two admin documents. So I'm going to go over and see if he is available if that's okay.

DR. MARKS: Sure. Yeah, I agree with you. Hair dye epi and then the aerosols and inhalation are the last two I have. And they're both in the admin section. And then we got, in Wave 3, the letter from the Women's Voices for the aerosols.

DR. ANSELL: That's an interesting reading.

DR. MARKS: And I don't think we got anything on any hair dye in the supplement.

DR. SLAGA: I didn't see anything.

DR. MARKS: Pardon?

DR. SLAGA: I didn't see anything either.

DR. MARKS: Yeah, okay. Let's go in the Admin Tab, and hair epidemiology. Okay, so let's go ahead to the revised draft, hair dye epidemiology document. There's a memo from Jinqiu, data November the 9th, in which he incorporated Dr. Naldi's comment, and they are highlighted in the text. That's Page 59. So, the memo is Page 30. Fifty-nine is the memo under the discussion. A lot of it's highlighted in yellow. Did we get anything more about the hair dye this morning?

MS. FIUME: Yes.

DR. MARKS: I thought there was another document. I don't know what I did with that. Thank you. Tom and Ron and Ron, did you see this? One of the issues the council had is description of "ideal epidemiologic study" in the discussion. And then talks about the discussion is not appropriate because it focuses only on breast cancer. A more general discussion of the epidemiology would be helpful. Did you see this, Tom? Were you able to read this?

DR. SLAGA: I'm looking for it right now. Yeah, I got it.

DR. MARKS: Good. Should we take a minute? Were you able to read it this morning?

DR. SLAGA: No. I didn't.

DR. MARKS: Okay. Well, then why don't we take a minute, because I don't think we can make recommendations without considering this memo.

DR. SHANK: I left them in the other room. That's why I don't have it here.

DR. MARKS: Yeah, okay. And I'll be giving you the next one on the aerosols. Why don't I give you that right now. Because this will be our next one after this.

DR. SHANK: Thank you.

DR. MARKS: You're welcome. Tom, you read it? Ron Hill, you're close?

DR. HILL: I'm essentially at the end.

DR. MARKS: Okay. So, we're on Page 59 in the Admin folder. And the first paragraph talks about linking hair dye use and breast cancer. And the council didn't feel that that focus, perhaps, was appropriate.

DR. SLAGA: I agree. It's too much focused on breast cancer.

DR. MARKS: How would you want to change that for Jinqiu? Obviously, we're going to see another draft of this. This is really important, obviously. Unless it will be a simple --

DR. SLAGA: Their comments are very good about adding, to the discussion, the aspect of the meta studies and all that. It should cover everything the document lays out. The discussion should revolve around that.

DR. MARKS: So are you, Tom, talking about -- again, are we still on the first paragraph in terms of the council suggests that it should be a more general discussion?

DR. SLAGA: Well, it includes everything. All the cancers, some pros and cons about all the cancers, not just breast cancer. They bring out about the meta-analysis and how that should be discussed.

DR. MARKS: So, you would follow the council's recommendations for edits?

DR. SLAGA: Right. Or the committee on hair dye -- the technical committee on hair dye.

DR. MARKS: Okay.

DR. HILL: Can I ask about their first paragraph? Again, I appreciate the fact that if new dye were to come along and it showed mutagenicity, it would be rejected at hand. But we do have legacy dyes that are out there under the Coal Tar exemption that are strongly suspected carcinogens if not known carcinogens.

I mean, over time I'd expect those to disappear because of the increased restrictions of the European market and that people don't like to just market in the US. But it's not accurate to say that we have no hair dyes on the market that are not known carcinogens. That's not correct.

DR. MARKS: Tom, your response?

DR. HILL: I mean, I'm just responding to their commentary as to how you'd interpret that first paragraph in the document that's being finalized.

DR. MARKS: Well, I don't think it's going to be finalized with this rendition. Because the council's suggestions from the hair coloring technical committee are significant. I think we'll need to, Jinqiu, see the next addition. We'll see what the Belsito team feels. But basically, Tom, you would agree take this as the format?

DR. SLAGA: Yeah. No. They have some very good points.

DR. MARKS: Both as far as the focus on breast cancer, it's sort of flipped around. And then the description of the ideal epidemiologic study, "Shows a fundamental misunderstanding around hair dye safety. Individual hair dyes are assessed for mutagenicity and potential carcinogenicity as part of their safety review. And a mutagenic hair dye would not be considered acceptable for use." This is what you're talking about.

DR. HILL: That's what I'm talking about.

DR. SHANK: It has been in the past.

DR. MARKS: Pardon?

DR. SHANK: We have reviewed hair dyes that have been mutagenic, and said that they could be used safely as a hair dye because of the rinse off, low exposure. Do we really want to get into the position of recommending specific parameters for epidemiologic studies?

DR. HILL: I don't think so.

DR. SLAGA: I don't think so either. I don't think that's our charge. I don't think we have the expertise to do that.

DR. ANSELL: It really wasn't the question that we thought we asked either. Did we feel that we had all these epi studies and we wanted someone who could kind of wrap the whole thing up for us?

DR. SHANK: Yes.

DR. ANSELL: And not propose what an ideal study would look like. You know, including a study of 356,590 women. So, I think we certainly agree with this.

DR. SHANK: Okay.

DR. ANSELL: Not in this framework document.

DR. SHANK: I don't think we should go there.

DR. HILL: I have interpreted his commentary to suggest that -- really as suggestions of, here's the problem with the existing studies and were one to construct an ideal study, this is what it would have to look like. But not necessarily that he was making a recommendation that we should say this is what needs to be done.

We did discuss, at least informally at that meeting as I recall, what would you have to do to get epidemiology to mean anything whatsoever. Which is where I made the comment, the only time I've seen even a reasonable whiff was in the occupational study in Chinese hairdressers, where there was a large population. And even there, there was not statistical power enough to detect it. And that was some 10,000 people if I remember right.

I think our whole take on that was, we aren't going to get any firm answer from epidemiology which is definitely nicely written in here. We have to keep paying attention to it for obvious reasons. Everything else in here, though, I agree with. This is a great analysis.

DR. SHANK: If you can't quantitate exposure, you're dead in the water. Sorry, but that's just the case. And you can say dark hair dyes, never used, once in a while used, all this stuff. It's going to get you nowhere. You just don't know what the exposure is.

DR. HILL: My feeling about this sort of thing is the same as my feeling about computer modeling. It's a reasonable hypothesis generator that you get, then used to turn around and say, how do we study this mechanistically? The difficulty there is that analysts are humans. As we improve our abilities to do cell-based studies and try to interpret those, and translate those, we could at least do better and better mechanistic studies. Which in some cases we'll say, no there can't possibly be a connection. Best we can tell within the limits of science.

DR. SHANK: You can't say that.

DR. HILL: No, you never can.

DR. SHANK: That there can't be --

DR. HILL: I didn't state that the way I intended it, but --

DR. MARKS: So, with that in mind, on Page 59, the paragraph which states this is an ideal -- we're suggesting what the ideal epidemiologic study is, you would delete that whole paragraph?

DR. SHANK: Well, I would. Certainly don't call it "the ideal."

DR. SLAGA: Yeah. Nothing's ideal.

DR. MARKS: I hear that. I mean, we could --

DR. SHANK: I would leave it out entirely. I don't think --

DR. MARKS: Yeah. Because it gets back to your point of are we the one recommending what the study should be.

DR. SHANK: Right.

DR. MARKS: Now we could certainly have, in a discussion, about your point, Ron Shank, of a quantitative exposure has got to be crucial. I don't know if we want to --

DR. SHANK: Yeah. I mean, it's half of the equation.

DR. ANSELL: Or the difficulties of doing epi in this arena. But I think the document is intended to be kind of an overview. This was more of a letter -- or a proposal, as opposed to contributing to an overall assessment of hair dyes that we continually work on.

DR. SHANK: I think the way it started out, originally, is this is a summary of the data of epidemiological studies. We have 42 or 57 or 900, these are all of the studies that have been done, a compilation. And the end result is, there is no clear established relationship between hair dye use and cancer in the human population. And if you want to say, yet.

DR. ANSELL: And that's where we struggle, is how this yellow -- the added text contributes anything to that discussion.

DR. SHANK: I think it should just be, this is a boilerplate not a whitepaper on hair epidemiology.

DR. MARKS: Yeah. And as I recall, Ron, exactly what you said. And, periodically, we would update, it with these newer studies, to indicate that the panel had looked at the studies.

DR. SHANK: Right.

DR. MARKS: And evaluated them. So, this whole -- on Page 59 where the council made -- and, Tom, you agree that it should be broader than breast cancer. I'm trying to think, then what would we have under the discussion, just that?

DR. HILL: How about the first two paragraphs with some modifications of the second one.

DR. MARKS: I mean, ultimately the -- let me see. Let me go back here, 59. But it's constructed that we had the discussion, but the point -- and you have, Jinqiu, all these studies you mention ahead, but isn't right in the beginning. Then you go over the various cancers in the boilerplate, prostate, leukemia. The study summary. That was where it was continuously being updated with the new studies. And then background. We don't have a conclusion, do we?

DR. SHANK: No. Well, the conclusion is --

DR. ZHU: Page 60.

DR. ANSELL: Is unchanged.

DR. MARKS: Yeah. The conclusion is on Page 60. The panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer.

DR. SHANK: Right.

DR. SLAGA: Right.

DR. MARKS: The associations and other findings are lacking in strength and consistency. In addition, the panel noted there was no consistent pattern of genotype/phenotype influence on hair dye epidemiology findings. That's the conclusion as we have it.

DR. SHANK: Okay, the first half of it is fine. Where is that?

DR. MARKS: Page 60. Right at the top.

DR. SHANK: The conclusion?

DR. MARKS: Yes. I don't know that the last sentence is necessary.

DR. MARKS: Yeah.

DR. HILL: My interpretation of its presence there is just that that was not considered in the previous iteration of this document. And that it was looked at, but maybe that's not the right place to put it.

DR. ANSELL: Right.

DR. HILL: And if you figure out what actually should go in the discussion, maybe that would be in there.

DR. SLAGA: We could just leave that last sentence out. The first sentence is really the important one.

DR. SHANK: Yes.

DR. ANSELL: Yeah.

DR. SLAGA: It summarizes all of the studies.

DR. SHANK: Sorry. I mean, all that work -- a very nice analysis prepared. But for a boilerplate, I think, it's not necessary. And if you want to write a position paper or whitepaper, whatever you want to call it, as a statement of the panel, or a statement of the CIR, or a statement of the council, that's a different document. And then you can get involved in all the different parameters that effect exposure and effect --

MS. FIUME: So, Jinqiu, to clarify, the discussion is for the precedence document that goes on the website. This isn't discussion language in the report document itself, is it? It's is the discussion of the precedence paper? Is that correct? And the report will just refer people to the precedence paper?

DR. ZHU: Yeah.

MS. FIUME: Yeah. So that discussion language isn't being proposed for inclusion in the report itself; it's the discussion that goes with this whole precedence document.

DR. MARKS: Oh yeah, we understand that.

MS. FIUME: Oh, okay. I just wanted to make sure, okay.

DR. SHANK: That being the case, then you need to expand it in great detail.

DR. ANSELL: Or delete it all, because it doesn't have anything to do with precedence either.

DR. MARKS: Yeah. So, that was my next question is, do we even need a discussion? Because we're updating every -- with the studies. Now, Jinqiu, all the discussion on the studies, preceding the discussion, they are repeated in the table below, correct?

DR. ZHU: Yeah.

DR. MARKS: Yeah. Okay. So, what you do in the text portion of it, you're just expanding the table. I mean, none of the questions would be --

DR. ZHU: Yeah.

DR. MARKS: Do you need -- again as, I guess, a position paper -- do you need more than the conclusion and the table in the references?

DR. SHANK: I think we're talking about two very different things.

DR. MARKS: A boilerplate, I'm sorry.

DR. SHANK: The table is great.

DR. MARKS: Yeah. I agree. What I'm wondering is -- the table's redundant to what's in the text prior to the discussion, do we really need the text?

DR. ANSELL: In this, I think, the background, on PDF 53, the following provides a brief summary of what's come out since the last time we did this.

DR. MARKS: Right.

DR. ANSELL: And then to the extent that it doesn't change any of your conclusions --

DR. MARKS: So, you're fine leaving the text in and then having the table, which is a summary of it.

DR. SLAGA: Yeah.

DR. MARKS: Okay.

DR. ANSELL: Striking all of the --

DR. MARKS: Discussion?

DR. ANSELL: Yeah.

DR. HILL: What don't you like about the first two paragraphs of the proposed discussion, which kind of recaps and distills concisely?

DR. SHANK: To narrow.

DR. HILL: To narrow?

DR. SHANK: Yes.

DR. MARKS: Yeah. It starts right off the bat by saying -- linking hair dye use and breast cancer is limited. I mean, it's really between hair dye use and cancer, period.

DR. SLAGA: Right, period.

DR. HILL: So what if you take out that first sentence and start reading from two systematic reviews, three case-control studies and one cohort study?

DR. ANSELL: Because there's more than that.

DR. MARKS: "All published since 2004 were evaluated for --"

DR. ANSELL: Yeah. I mean, then you leave out anything that isn't involved with the breast. That statement is specific to breast cancer.

DR. SHANK: What we've done is just review all of the studies that are out there, published mostly. That's it. And we can't conclude a cause and effect relationship. All of this other stuff is unnecessary.

DR. MARKS: Yeah. So it would be a very short discussion.

DR. ANSELL: Yeah. Because the purpose, as stated in the introduction, is we did this last in 2010, and here's what's been published since that time. And looking at bladder and prostate and leukemia --

DR. SLAGA: Lymphomas.

DR. ANSELL: Lipomas, breast cancers. And then we determined that the available evidence do not provide sufficient evidence for causal relationship. I think that's a --

DR. SHANK: That's where I'd go.

DR. MARKS: Which is essentially what we say in the conclusion.

DR. SHANK: Yes.

DR. MARKS: Do we need a discussion?

DR. SHANK: No.

DR. MARKS: Is it important, all the references we have there's not, Jinqiu -- the reference to the external expert, in the epidemiology field, is that important to capture? Because that wouldn't be in the table, is it?

DR. SHANK: That would not be in the table.

DR. ANSELL: Because he didn't actually do one.

DR. MARKS: No. So, I mean, is it important to reference that we had an external, or that will just appear in the minutes of our meetings. And that we did look at Naldi's review. Again, I only raise this because this will be the boilerplate, which now will be in place for probably another decade. And is it important to capture that we --

DR. ANSELL: But he didn't do --

DR. MARKS: No. He didn't do any of these, he just reviewed things.

DR. ANSELL: Well, he's proposing what an ideal study for breast cancer might look like.

DR. MARKS: Oh yeah. Exactly. Which we're deleting.

DR. ANSELL: But what we wanted him to do, I think, was to take a look at all the new stuff, as an epi expert, and see whether it changed our 2010 conclusion.

DR. MARKS: Right.

DR. ANSELL: And what he did, was come back and said well, no; but if we wanted to know a real answer, here's what he would propose.

DR. MARKS: Yes.

DR. ANSELL: So, I don't see it contributing to this. I don't think we should lose it. If anyone wants to fund the 400,000 women study, I'm sure he'd be happy to --

DR. SHANK: For each hair dye?

DR. ANSELL: And only breast cancer.

DR. SHANK: And only breast cancer?

DR. ANSELL: Yeah. So, we'll have one ready.

DR. MARKS: So, my sense is we just delete the entire discussion; and that addresses the issues that the council brought up?

DR. SHANK: That's where I'd go. In the beginning we say how we reviewed all these studies, summarized in table one.

DR. ANSELL: Yeah. You could add to the conclusion that we reviewed all the studies above.

DR. MARKS: Yeah, I'm not sure it's worth it, because the conclusion covers that.

DR. ANSELL: Yeah.

DR. SHANK: Yeah.

DR. MARKS: We'll see how it goes tomorrow, but I'm going to put delete discussion.

DR. SHANK: Maybe I'll have to leave early.

DR. MARKS: Well, no. It'll be done in a professional way. And we'll see what the Belsito team feels. I mean, they may want to expand. Delete discussion. Okay.

DR. SHANK: Great.

DR. MARKS: That addresses the issue of broader than breast cancer. And it addresses, also, the ideal study issue. And we'll see.

DR. SLAGA: Sounds good.

DR. MARKS: Any other comments? Thanks.

DR. HILL: I'm actually shutting my mouth and rereading all of this, so that I knew exactly what it said. I now concur.

DR. MARKS: Okay. Next is the aerosols and inhalation. And I'll be recommending that and I think that's our last one. So, with that in mind if we just delete the discussion, we're at the final boilerplate. Because there's no need to reread. Other than we're going to delete the discussion, we're modifying the conclusion. Because we're deleting that sentence in the conclusion, Ron Shank, you had asked.

DR. SHANK: When did we start using precedent documents? After?

MS. FIUME: A while.

DR. SHANK: Really?

MS. FIUME: They're on our website that way.

DR. SHANK: As precedent documents?

MS. FIUME: Because the term boilerplate and framework didn't fit; because it's not a boilerplate, it's a resource document, actually, is what it's called.

DR. SHANK: Yes.

MS. FIUME: It's a resource document. And so, the discussion refers to the resource document link. Where everyone can go and see why we say what we say about hair dyes, or inhalation information.

DR. SHANK: Okay. And now that's called a precedent?

MS. FIUME: Resource document.

DR. SHANK: Resource?

MS. FIUME: Yes. It's probably been at least four to five years.

DR. SHANK: I'm a slow learner. Okay.

DR. ANSELL: Well, this is significantly different than the resource document for pesticides and natural products. So, I could see why this would not pop out, instantly, as the type of thing we've been doing for a long time.

DR. HILL: Well, in part because we review a hair dye once a year. All though, of course, I don't come to a couple meetings.

DR. MARKS: Okay. So, for the hair dye epidemiology, I'm going to propose, tomorrow, after the Belsito team has commented, that indeed we did take into consideration the technical committee's recommendations for editing the discussion. And we felt the best way to edit the discussion is to delete it. And then we also wanted to delete a sentence in the conclusion on Page 60, and I'll read that. That's the second one, second sentence. So, I'll read that tomorrow. That's Page 60. Okay.

That was an interesting -- and then the resource document, we have a history of that, but I won't repeat that. I think it is different with the hair epidemiology, because there's so much epidemiology studies that come out. Hot topic, so to speak, so in contrast -- to some of the other. That's why I think it's updated. And I like the way -- the table, I think, it's very good in summarizing it. Go ahead, Ron Hill.

DR. HILL: You said the second sentence, but there are three sentences.

DR. MARKS: Oh, are there? I'm sorry.

DR. HILL: The one with the no consistent pattern of genotype/phenotype influence.

DR. SLAGA: Yeah.

DR. HILL: Is that the one that we're taking out?

DR. MARKS: Yes.

DR. HILL: Okay.

DR. MARKS: The last two sentences. I'm sorry, you're right. We weren't going to do, "The association and other findings are lacking in strength and consistency." Were we going to delete that? And just leave the first sentence, "The CIR expert panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer." And that's it. Yeah, thanks for clarifying it. It's the last two sentences.

DR. HILL: Because tomorrow you'll be going fast and --

DR. MARKS: I won't be going fast. I would hope tomorrow you would say the same thing.

DR. HILL: You'll be reading your notes and then create confusion.

DR. MARKS: Yeah, you got that right. I will definitely be reading my notes. Delete two sentences.

MS. FIUME: And can I just clarify. I think someone had said those were new sentences. At least that last sentence. That's been there since 2014.

DR. HILL: The genotype/phenotype was in there?

MS. FIUME: Yes.

DR. HILL: Okay, it's not new.

MS. FIUME: Just so you know, it's not a new sentence.

DR. HILL: That was me. Okay.

DR. MARKS: Okay, thanks. That's what we'll recommend tomorrow. I like it cleaner with just the one sentence. Okay, any other comments? If not we'll move on to the aerosols and inhalation.

Dr. Belsito Team - December 3, 2018

DR. BELSITO: So, hair dye epidemiology is next. That's in the admin book. And then we got another handout this morning, is that correct?

DR. LIEBLER: It starts on page 30. It's the memo.

DR. BELSITO: I thought it was good. I really didn't have any comments. It looks like the council had some. Description of the ideal epidemiologic study in discussion section includes recording use concentration of all -- I did not have any comments, the council had some. And maybe you want to comment on your comments, rather than my reading them?

DR. BERGFELD: Well, there's a lot of them.

DR. EISENMANN: The comments are coming from the Hair Coloring Technical Committee. They reviewed it. And they're a little concerned about Dr. Naldi's comment, that before doing the epidemiology you should look at what components are carcinogenic and mutagenic. The industry does not put carcinogenic or mutagenic hair dyes into hair dyes.

There was an agreement, way back in 2003, in Europe to do a certain standard set of mutagenicity studies on hair dyes, which are being done now. And US hair dyes are very similar to what are used in the European market.

The other concern is with the discussion. It's more or less the discussion focuses just on breast cancer, and we don't think that that should be the focus. In general, for epidemiology studies, fairly common exposures and fairly common cancers will come up with an association. Another evidence is that you have a positive prostate cancer study, and you don't mention that at all either, in the discussion.

We want to be clear that epidemiology is one tool, and that you also have to look at the genotoxicity potential of the hair dyes and exposure. And whether or not the study suggested, by Dr. Naldi, should even be mentioned, is also a concern because it's such a large -- yes, and nice power calculation on how many people you would need to show an association, but it's pretty unrealistic. No one is ever going to do such a large study like that.

And then if you leave it in the document -- I'm not sure if it came through an email, or how you go the information from Dr. Naldi, but I didn't see it other than cited in the report. So, everything needs to be publically available. So, the email has to be put out somewhere publicly rather than just to cite.

DR. ZHU: But that's like a short email. Dr. Naldi refers to new, published meta-analysis paper. So all the future investigations, all the studies, are coming from that paper, which it was cited in there.

DR. EISENMANN: Okay. Well, that wasn't clear from --

DR. ZHU: It was cited in the document. It was cited in the paper.

DR. EISENMANN: It sounded like it was coming from Dr. Naldi.

DR. LIEBLER: That's the impression I got, too.

DR. ZHU: Oh, okay.

DR. LIEBLER: Even though you did have a citation in there. The way the introduction memo was developed, from you describing the response, it sounded like it was just -- you know, you asked him, what should an idea study be like.

DR. ZHU: So you mean we need to mention this information directly --

DR. LIEBLER: I'm not sure this even belongs in this discussion.

DR. BERGFELD: I don't think so either.

DR. KLAASSEN: Yeah. I didn't think so either.

DR. BERGFELD: I think it needs to come out. That's an academic discussion.

DR. LIEBLER: Right. For all the things that Carol says, the punch line is this really needs to go.

DR. ZHU: So, one question. Do we need to maybe discuss the different types of cancer individually? Because we have already concluded, in the conclusion section, there is no kind of relationship between hair dye user and cancer. Because for some specific type of cancer, we only have one or two studies. In that case, do we still need to discuss that specific type of cancer?

DR. EISENMANN: My feeling is that you wouldn't have to discuss each and every one. But some more general things about epidemiology.

DR. ZHU: But in the council's memo, it indicates that the discussion should clearly state that epidemiology will never prove that hair dyes do not cause cancer.

DR. EISENMANN: Right.

DR. ZHU: Do we need to include that information?

MR. GREMILLION: Dr. Naldi was brought on in response to the study showing a correlation with breast cancer specifically. Is that --

DR. LIEBLER: He was brought in to provide an epidemiologist perspective on the inconsistent body of data, with respect to breast cancer incidence and hair dye use epidemiology. So, there are some studies that indicate an association and other studies that indicate no association.

MR. GREMILLION: Yeah. I guess my point was, his comments directly address breast cancer. And so, it seems fitting that the discussion would focus on breast cancer a little bit and not --

DR. LIEBLER: Well, the discussion could certainly address breast cancer. And there's more epi data on breast cancer in hair dyes, and I think any of the other cancers.

DR. BELSITO: Bladder cancer.

DR. EISENMANN: Well, it should also be noted this doesn't contain all of the epidemiology. This is just still some of it. But there's some earlier studies, still, I believe, that are not here. The focus of this has always been since the IARC review. You picked up a few of the older studies now I believe. But I still don't think it's completely comprehensive.

DR. LIEBLER: I think our feeling is that the third paragraph of the discussion, it has the description for what would be the ideal epi study for breast cancer. It doesn't really belong here. Because we're not prescribing any other epi, basically. I think it's better for us to say that epidemiologic studies will continue, and that the panel will monitor them and continue to include them in our safety assessment.

DR. BELSITO: Yeah. But I think the discussion goes off base, because breast cancer is only one of the endpoints that we looked at. And it's the only thing in the discussion, number one. And number two, do we need a discussion at all? I mean, we've looked at all the

data. And there's sort of the discussion as part of the data we look at. And then it's just a conclusion; as we state, the data do not support it. I mean, why do we need a discussion at all for this statement?

DR. SNYDER: So I wanted to eliminate almost all of the discussion. And only just state -- this is our discussion. It's not Dr. Naldi's, it's our discussion. And so, I thought we should start off by saying that we continue to do our due diligence, periodically reviewing the literature. And then these studies came up. We reviewed these studies. We had an expert look at them, and advise us if there was any issues. And they are problematic as all the previous epidemiologic studies are, with compounding factors, and other issues related to phenotype, genotype, and all the things we discussed before. But that can be very general or broad statements.

And then I thought we needed to revise the conclusion because, I think, the conclusion we can't use vague terminology. So, I mean, that we reviewed the currently available hair dye epidemiology, and they do not provide sufficient evidence for association.

And then we can't say, "and other findings." That's too vague a language. I think we should use some specific language. Like what are the other findings, like genotype, phenotype; which, I think, is what you're meaning in the second sentence. So you could actually bring that into the conclusion, first sentence. And just have one succinct statement saying that, again, "we review the current literature. Their association are weak at best."

I wouldn't put even that. And I wouldn't put anything in there about the ideal epidemiologic study, because that's our discussion, we're not qualified to put that out there. And I don't think that we want to promote other studies to be done. We're evaluating the literature as it becomes available, periodically.

DR. BELSITO: I didn't think we needed the discussion, or the second sentence of the conclusion. Because the second sentence of the conclusion is basically the first sentence, that the data do not provide sufficient evidence. And that the panel noted there are no consistent pattern of genotype/phenotype influence, period.

MR. GREMILLION: I guess I'm surprised because I felt like the discussion was meant to underscore some of the uncertainty. I was going to push back, looking back at Dr. Naldi's comments. There's this line in the second paragraph of the discussion, "based on the available human evidence, personal use of hair dyes is unlikely to be an important risk factor for breast cancer." And then it goes on.

And Dr. Naldi's comments, he follows that up with, "however, of particular concern are two recent studies pointing to an increase risk in different ethnic groups and populations." I think that's helpful to underscore some of the uncertainty out there; and to highlight at least, in those studies, there was this association found.

DR. BELSITO: But if you're going to do that, we're focusing on breast cancer. The one cancer that's been somewhat more linked, in terms of hairdressers, is bladder cancer, and we're not discussing that at all. We basically would have to reiterate everything we've already said, pointing out that non-Hodgkin's lymphoma, bladder cancer, breast cancer, glioma, da-da-da, da-da-da, da-da-da.

For some reason Dr. Naldi elected to focus only on breast cancer, which really comes out of a single paper that looked at African American women having higher rates of breast cancer in association with hair dye. For which there was very little data as to the hair dye. And the thought, I think, there was obviously this is a dark color hair, this is para-phenylenediamine or whatever.

And people have always looked at hair color, dark or light. But I just don't think that a position paper like this, we basically -- the discussion is contained in each of the different cancer endpoints we looked at. And so, we've looked at each of the cancer endpoints. We've had the discussion in there.

And then all we need is a conclusion from that, is when you look across all of the different types of cancer endpoints, from bladder, to prostate, to glioma, da-da-da, the data is insufficient. There does not seem to be an association with any of these. That's our conclusion.

DR. GREMILLION: His comments talk about different ethnic groups and populations, African Americans, white American women, Finnish women. So, he's referring to more than just one study of African American women.

DR. BERGFELD: Can I ask a question? Is it your inference, Carol, that we should go back and collect those old reviews and put them in here? Because you said we didn't have them.

DR. EISENMANN: No. I don't think it's necessary. You're relying on the IARC review for the older studies, which I think is appropriate. I'm not sure that you would want to go back and look at all the older studies. You're looking from the IARC on. Except for, I think, we went back a little bit for the breast cancer studies. That was the intent from IARC on.

DR. BERGFELD: Do you have anywhere we say that?

DR. EISENMANN: Yeah. It says it in the introduction, I believe.

DR. KLAASSEN: I can look. On page 53.

DR. LIEBLER: I think I support deleting the discussion; trimming the second sentence out of the conclusion, and finalizing the document.

DR. BERGFELD: As a 2018 document?

DR. LIEBLER: Yes.

DR. BERGFELD: And anywhere do we have that date into this document? Is it going to be led by 12/2018 on the source document, the title?

MS. FIUME: Yes. It's on the front page of it. PDF Page 52 is the front page for the resource document; and that will have the date on it there.

DR. BELSITO: So, Dan, what are you telling me about what you want to do with the discussion? Where are you saying that -- in the introduction, that this was to be a focus on breast cancer?

DR. LIEBLER: No. No. I was referring to PDF Page 59, which is all yellow-highlighted discussion; which included that description of a putative ideal epi study for breast cancer. That entire discussion's about breast cancer.

DR. BELSITO: Right.

DR. LIEBLER: And I think that's inappropriate in this document.

DR. BELSITO: That it's what?

DR. LIEBLER: That it's inappropriate in this document.

DR. BELSITO: Yeah. Well, that's what I was saying.

DR. LIEBLER: So, I'm basically agreeing with you. I was sort of seconding what I took to be your suggestion of what to do with this. Is that we take out the discussion and we take out the second sentence of the conclusion?

DR. BELSITO: Yeah. And just in the conclusion say that we will continue to monitor data.

DR. LIEBLER: Correct.

DR. BELSITO: I was the one who recommended Luigi. I forget why Bart sent out an email looking for an epidemiologist. Was it specifically for the breast cancer study? What did he ask Luigi to do?

MS. FIUME: I don't remember. Jinqiu, do you know what was asked?

DR. ZHU: Specifically, for breast cancer. I remember.

DR. LIEBLER: We had the largest body of data, and it was the one where we felt there was inconsistency that needed to be addressed by the panel. And we didn't feel that we were -- amongst the panel, ourselves, we had the right expertise to deal with that question.

DR. BELSITO: And his response was, based on the available data that there did not appear to be a causal relationship. And then he went on to this big thing about, well, to really know you need to do this huge --

DR. SNYDER: We need 356,000 patients, with these criteria, blah, blah, blah.

DR. BELSITO: Right. So, we got his answer; that, at least, based upon the data that exist today, there appears to be no causal relationship.

DR. LIEBLER: Right. I think it was either -- in the previous iteration of this document, because either a comment from somebody on the panel, or possibly from the council, I don't remember which, saying it would be better to say what should be done. Or it would be useful to say what should be done. I don't remember where that came from, but I do remember the request from somebody.

And that led to this discussion, I think, particularly, the third paragraph of this discussion. But basically saying, a huge, super, uber, epi study is not going to -- first of all, it won't ever happen. And even if it did, it probably won't answer the question beyond any possible doubt.

MR. GREMILLION: I guess just reading Dr. Naldi's study, and the concise summary statements there he has -- the first sentence, "the available evidence linking hair dye use and breast cancer is limited, but warrants further investigation." I remember in a previous meeting we had, the available -- just the first clause of that sentence.

And I feel like it's a similar -- even though they're set out in two sentences, it's a similar kind of package of statement. Saying, based on the evidence, it's unlikely to be an important risk factor; however, of particular concern are these studies. And then he concludes with the need for a systematic review.

DR. SNYDER: I took that in the context of his expertise as an epidemiologist. This is our document. And so, in the context of the data that we review, we have not been provided any substantive data to make us be concerned. And we don't really want to be -- we want to be cautious about promoting studies, because then somebody says, well, what kind of study? And we're not qualified to do that. And so, again, I think that's what we're trying to do.

MR. GREMILLION: It is. And honestly, if the discussion section gets deleted altogether, it's a moot point. But my objection was just having that, based on the available with human evidence sentence, without the following sentence, that seems to hedge it a little bit.

DR. SNYDER: I think that's what Don was saying in the conclusion we have, that to date there's no human data to support a cause and effect relationship.

MR. GREMILLION: Yeah. I mean, specifically in the discussion he's cited for that first line. But yeah, I understand you have your own analysis and you're going to present it.

DR. BELSITO: But I mean, he takes and he says, okay, the ideal epidemiologic study to evaluate breast cancer. Then we should say, the ideal epidemiologic study to evaluate lymphoma. The ideal epidemiologic study to evaluate bladder cancer. The ideal epidemiologic study to evaluate glioma. We could go on and on and on.

And basically, I think that our point is, we've looked at all the studies, there doesn't seem to be a causal relationship; but, we will continue to monitor everything that comes out in the literature. That's all we can do.

MR. GREMILLION: I don't want to say a description of the needed study needs to be in there. I'm not familiar enough with these reports. But I do think that there's a basis for singling out breast cancer, based on the same factors that led you to get Dr. Naldi in the first place.

DR. BELSITO: Again, I think if we're going to single out a cancer, we'd single out bladder cancer.

MR. GREMILLION: The studies on that are for the workers.

DR. BELSITO: The studies for users do not show a causal relationship. But there is suggestoid (phonetic) evidence for hairdressers.

DR. SNYDER: Certain genotypes.

DR. BELSITO: Certain genotypes for hairdressers. And there's also the confusion with a confounder of smoking, which is also known to be carcinogenic. And the same thing came up in the textile industry when it was in the US. Textile dye workers, and smokers, and bladder cancer in that industry. So there's suggestoid evidence for those groups.

So, if there's any cancer that seems like it could be related to dye, it would be bladder cancer, more than breast, or lymphoma, or prostate. Because you never really saw prostate cancers coming up in the textile workers, who were largely men.

I just think that by putting this discussion in at all, I mean you just have to go on, and on, and on to look at all the cancer types.

DR. SNYDER: Well, I think you said, earlier, that this discussion, much of it could go under the breast cancer, dealing with that new study that we raise our first concern. So, it's not like we're going to throw it all out. It's just that it's not appropriate in a discussion for an overarching document to just focus on one cancer.

I think we can take some of that language and move it under the breast cancer, particularly, in relationship to the interpretation of that study that showed something that we were not comfortable with interpreting. And that's why we had the expert come in.

DR. BELSITO: Actually, that's a good point. I mean, this goes under the breast cancer part, not a discussion for the entire document. And can be condensed a little bit.

MS. FIUME: I think Jinqiu can take the suggestions given and then rework the document a little bit. And remove the discussion and make it what you want it to be.

DR. ZHU: Yes.

DR. BELSITO: I don't think there is a discussion to this document. The discussions occur in each of the sections of cancer.

MS. FIUME: Right. Move it from the discussion into the cancer section. Because in the past versions, whatever we've included in the report, we've never specified a specific cancer. It was just hair dye and cancer. It was never any type of specific cancer mentioned. In the wordings of our reports, we always refer to our resource document, which we will do as normal. But we've never specified any type of specific cancer, in either the summary or the discussion sections.

DR. SNYDER: My only comment was that I thought it was a good mechanism to make the reader aware. They don't have to read through all of the cancer publications to see where we're at, as far as how current are we.

So, I thought it was okay to have a brief discussion that said we've identified -- since 2014, the last time it was reviewed, we've identified these five additional studies, they were considered, and just leave it at that. And the conclusion is still what it is.

I just thought that was maybe a good way to let the reader know what we looked at and some interested party could say, well, you missed this study or something.

DR. BELSITO: Okay. So this will come back to us once again?

MS. FIUME: Yes. For a final, final look.

DR. BELSITO: Okay.

DR. BERGFELD: Will it go out for comment again?

MS. FIUME: Did it go out for comment last time, Jinqiu, or are we waiting until we get it all finalized? I guess it did go to comment because it's a public document. I forget how it worked. I'll check and see what we did and we'll follow the same protocol.

DR. BERGFELD: Yeah. I think it goes for comment.

Full Panel - December 4, 2018

DR. BELSITO: It was my request that we update this, simply, because we hadn't updated it for a while and there was new information out. I think the particularly more disturbing one was the apparent higher rates of breast cancer in African-American women, using hair dyes, versus non-African American.

We had asked Dr. Luigi Naldi, from Bergamo, Italy, to look at that data. Overall, he did. And he found that the available evidence, linking hair dye use and breast cancer, was limited; although, he did feel that required further investigation. At this point, he said, based upon the available evidence, he was not seeing a link.

Our only concern was that his report ended up in the discussion, as a full report, dealing only with breast cancer, and that's not the only cancer we're concerned about. We had recommended that that entire highlighted area in the discussion be deleted, and just sort of summarize; that based upon the available evidence, there is no apparent causal link between consumer hair dye use and carcinogenic endpoints of any kind.

DR. BERGFELD: Any comment?

DR. MARKS: Yeah, we agree, wholeheartedly, with what you suggested, Don. Let's go to Page 60 of the document. Because the other thing that we felt, that the conclusion on Page 60, that the last two sentences on the conclusion were not necessary. So, our conclusion would be just, that the epidemiology data do not provide sufficient evidence for causal relationship between personal hair dye use and cancer. And delete the second two sentences. We felt that they didn't add anything and, in fact, they may confuse the issue.

DR. BELSITO: I don't have a problem with that, team? Okay. The only other thing to mention, in the discussion is, obviously, that we will continue to monitor this. And as new studies come out, we will look at them and reevaluate our conclusions.

DR. BERGFELD: The question I had of Bart is, if the team members on both sides or the whole panel are agreeable to these changes, that have been made, is this document ready to be posted? Or do we want to look at it one more time in April? This should be on a calendar review, at least every two years; and, obviously, if a report comes up, we should look at it right away. So, what is your suggestion?

DR. BELSITO: I think the changes we're asking for are so minimal, that this can go out as a final.

DR. BERGFELD: Okay. Jim.

DR. MARKS: I would second that. And, I guess, one of the reasons we deleted the discussion was because it wasn't broad enough and such. If we're reviewing new epidemiologic papers, or studies, as they occur, that do we really need the review -- that should be added to the document, ongoing, I would think, just like both in the text and in the table. And for us, every two years, to go back and look at this unless something really changes our conclusion. I don't know if two years is right or five years. Two years might be too often, but I don't know.

DR. BELSITO: I think we have a group of experts in various areas that will be picking up data. And if there's a substantive paper, that comes out, we should not wait two or five years. It should be brought to the attention of the panel. And then the decision can be made, based upon that, whether we need to update the document, or it can be held. But I don't think we should set timelines for this; because this is a very critical, topical, issue that needs to be monitored.

DR. MARKS: I agree with that approach, Don. I was just thinking you go from the beginning to the end with the document. I think that will occur naturally, as the new studies come in; and then they just get added to the document.

DR. BERGFELD: Well, one of the problems that we've had, historically, is that unless there is a big article or some publication that brings it to light that we need to look at, this particular document gets buried a little bit because of the workload internally. So, at least, if it's on the calendar, someone will take a look, quickly, at what's out there, so that we don't miss anything. That's something that can be decided internally how they're going to do that.

I'd like a consensus show of how you'd like to deal with this. And what I've heard is that it's ready to go and be posted. Is that correct?

DR. MARKS: That's correct.

DR. BERGFELD: All right. So, we'll do that. So, this will not appear in April. The next one is aerosols in inhalation. Dr. Marks giving his opinion and his team's opinion.

MARCH 2021 PANEL MEETING

Dr. Belsito Team - March 11, 2021

DR. BELSITO: So hair dye epidemiology, that’s in admin. Okay. Does anyone know what page this is on? Because I’m going through -- oh. Here we go.

DR. SNYDER: 52.

DR. BELSITO: Okay. Thank you. I should have written it down because you put in hair dye, and there’s a ton of stuff. Okay.

MR. ZHU: Good afternoon. Jinqiu is here.

DR. BELSITO: Hi. How are you?

MR. ZHU: Thank you. Great. Thank you. How are you?

DR. BELSITO: Good, thanks. I thought it was fine. I didn’t have any comments on it. I mean, I did like Wave 3, the Council response. I don’t know who put together that re-analysis of the incidence in African American women. But I thought that was very helpful and maybe should be brought into this report. Did everyone see that?

DR. SNYDER: Yes.

DR. SNYDER: Yes.

DR. LIEBLER: Yes. I did. I agree. I thought -- I agree.

DR. BELSITO: So that would be the only thing. I would bring in that analysis about the -- particularly given the years of association, which usually don't make sense because almost all the other endpoints where there seems to be an association were pre-1980. And then I also liked the idea about the births and children. Where it says parents, that really should be mother, right? I would think. But otherwise, I thought it was fine. Any other comments?

DR. SNYDER: I just had a couple small issues. On page 55, the third paragraph on this -- this is the Rollison score here. And we don't mention it here, but this is the Rollison score. Yet for every study, we talk about the Rollison score at the end of the study. And we don't mention that this is the system scale used here. So somehow we need to indicate that this is the Rollison score.

MR. ZHU: Sure. Will do.

DR. SNYDER: Do you see where I'm talking about, the third paragraph on page 55 under "Background"?

MR. ZHU: Yes.

DR. SNYDER: And then I would -- this, again, is just a style thing, but I would prefer that each study summary ended with whether or not -- what the bottom line was, whether there was an association or not an association, and not with the Rollison score. I think the Rollison score should be moved up after you go through the criteria for the epidemiologic -- the criteria for the epidemiologic study, then give the Rollison score instead of -- because the Rollison score is just a score on how predictive the data is.

I'd rather end the individual study summaries with the bottom line of whether there was an increased risk or no increased risk. And so they all end with a Rollison score. I don't think we should do that.

MR. ZHU: So you mean remove all the sentence for each summary -- the Rollison score?

DR. SNYDER: No. Keep the Rollison score, just move it up after you talk about the -- like in the first one here, the prospective cohort study.

DR. BELSITO: What page are you on, Paul?

DR. SNYDER: I'm on page 56, the first study there -- the first one that's yellow, the highlighted one. If you look at that first -- that prospective cohort study, at the end it says this hair dye exposure assessment was +3 on the Rollison scale. So I would rather have that be a -- that's part of the methodologies in what the -- the overall conclusion is that there was no association here. So I'd rather have what the main study conclusion was in regards to our issue rather than the Rollison score. We don't make a decision based on the Rollison score as to whether it was relevant or not.

DR. KLAASSEN: So what -- okay. So you take the last sentence and make it what -- the --

DR. BELSITO: First sentence?

DR. KLAASSEN: -- third sentence?

DR. SNYDER: Yeah. After they talk during the 36 years follow up data collected, right before "Overall" it looks like because that ends how they categorize people: non-user, less than 30 years, more than 30 years. And then have the Rollison score, and then the next sentence says "Overall, no association was identified."

MR. ZHU: Okay. So the Rollison score, move this sentence to the "Overall" -- ahead "Overall?"

DR. SNYDER: After the criteria and methodologies used to run the study.

MR. ZHU: Okay.

DR. SNYDER: And that's just my opinion because it looks like we just inserted all these at the end of these studies, and then it's not really -- we don't make the --

DR. BELSITO: So wait a minute, Paul. At which point are you putting that in? After the first sentence or after --

DR. SNYDER: Right before "Overall." Right before "Overall." They said "the data collection... use... detailed in duration" because all that goes into the Rollison score if you go back to the background.

DR. BELSITO: Okay.

DR. SNYDER: You know, assessed ever/never use, assessed type of hair dye, assessed dye type, assessed all four critical aspects. So after that data, then that's when we should give the Rollison score, in my opinion.

DR. BELSITO: So after the third sentence?

DR. SNYDER: Yes. Because for all the studies right now, it's at the end.

DR. KLAASSEN: He's actually saying after the fourth sentence, right before "Overall."

DR. SNYDER: Yes.

MR. HELDRETH: Would you then move the --

DR. BELSITO: Yeah. It would because the fourth sentence.

DR. SNYDER: Yes.

DR. BELSITO: It's after the third sentence. Because that third -- "During 36 years," that whole thing is one sentence.

DR. SNYDER: No. That's two there, "Data collection on permanent."

DR. BELSITO: Oh, yeah. I'm sorry. So it's after the fourth. You're right.

DR. SNYDER: Yeah.

MR. HELDRETH: Would you then move "Overall, no association," et cetera, down to be the last sentence?

DR. SNYDER: I would because that's the money shot. You know what I mean? All the rest of it is just the data, which is good. I think it should -- you know.

DR. BELSITO: Do you want to do this consistently throughout the report?

DR. SNYDER: Yeah. I think each study type we should talk about the cohort, the study, the Rollison score, and then the end of it, the last sentence should be really the money shot in regard to there was no association or whatever, so. Again, and you know, (audio skip).

DR. BELSITO: I like it, Paul. Dan, Curt?

DR. KLAASSEN: Yeah. I also like it. I was concerned about having this Rollison score at the end of all of these paragraphs, and I think it's much better early on.

DR. BELSITO: Right. And then it also makes you -- okay, this is a Rollison score 3. This is a really much better study than what we've seen in other studies, so I'm going to really pay attention to this data.

DR. SNYDER: Yeah. Exactly. Exactly. Because that's what I was using it as. I was like, okay. So how does this one rate in regards to the criteria?

DR. BELSITO: Yeah. I like it. That's great, Paul. Any other comments?

DR. SNYDER: No.

DR. BELSITO: Okay. Curt, Dan?

DR. KLAASSEN: No.

DR. LIEBLER: I'm fine with it, thank you.

DR. BELSITO: Okay. Great. Thanks, Paul. Okay.

Dr. Cohen Team - March 11, 2021

DR. COHEN: Okay. So our last item for the day is the hair dye resource document. What a tour de force that is. It's quite amazing. A lot of data in here. And this is Jinqiu's report, correct?

DR. ZHU: Yes.

DR. COHEN: And by the way, am I pronouncing it correctly -- your name correctly?

DR. ZHU: Perfect.

DR. COHEN: Okay. So we received the resource -- the document with a number of updates, and they were highlighted in yellow. Really, some interesting data. You know, I have some comments, but I want to open it up as well. I guess, just what I'll start off is the 117,000 women in the nurse's health program. They discuss small increase in basal cell carcinomas, and they lacked, "information on skin tone," although they -- what's that?

DR. BERGFELD: Critical.

DR. COHEN: Yeah. But I'll say, you know -- try to argue the flip-side, right? I said the same thing, Wilma. They have childhood reactions to the sun: lifetime blistering, moles, cumulative UV since their baseline. And 97 percent were Caucasians, and 12 percent were blonde or red-headed. And 30 percent were light blonde. So we might make some inferences there. It looked like they were using some modification of, like, last observation carried forward.

But I thought that conclusion was okay and was well-captured in the report here. I have a few others, but why don't we just circle the team for their comments? Tom, do you want to go?

DR. SLAGA: Yeah. Overall, the new data's research has been -- it falls in line with others. The only one that I had an OR very high -- almost 14 -- was women breastfeeding children increased childhood leukemia by that OR, which is pretty high. It's still not a causative, but I'm just pointing it out (audio skip). Hair dye use in women that then breastfeed children gives a fairly high OR.

DR. COHEN: Were they using hair dye at the time of breastfeeding?

DR. SLAGA: Hmm?

DR. COHEN: Were they using hair dye during the nursing period?

DR. SLAGA: It doesn't say for sure. It just said hair dye usage. You know, it didn't really say during, but that would even be used. Yeah.

DR. COHEN: So any comments about how it's placed in this report? Any concerns?

DR. SLAGA: No. No. The way it's stated in this report is fine, and it points it out. It's just a higher number than normal of all these other studies.

DR. COHEN: Got it. Lisa --

DR. SHANK: Okay.

DR. COHEN: Any others, Tom?

DR. SLAGA: No. That was the only one I really honed in on.

DR. SHANK: Go ahead and add the new studies to the document. But I'll have to repeat my comments of earlier. All of these studies lack sufficient exposure data to support the use of any hair dye --

DR. SLAGA: Right.

DR. SHANK: -- causatively related to the adaption of any cancer.

DR. SLAGA: Right. No. No. I didn't say it was causative. It's just the relationship that was a little scary.

DR. SHANK: Well, unless you know the -- if you rely on an old toxicology law, we need a dose response relationship.

DR. SLAGA: I totally agree with you, Ron.

DR. SHANK: And none of these studies give a dose response.

DR. SLAGA: Right.

DR. SHANK: And they pick all different kinds of cancers. So if you go back to the old days when people were trying to establish a link between cigarette smoking and lung cancer, it took a long, long time --

DR. SLAGA: Right.

DR. SHANK: -- to get sufficient data on exposure.

DR. SLAGA: Yeah.

DR. SHANK: And even that, the best exposure data wasn't very good. How many cigarettes do you smoke a day? All cigarettes aren't the same. A lot of fuzziness in that relationship.

But the overwhelming studies did support the same exposure type at least and lung cell cancer. I have a couple other examples. I won't bother with them. I think we can add -- it's a good idea to add all of these studies --

DR. SLAGA: Right.

DR. SHANK: -- to the report because it is building a library. Somebody questioned about expanding the table called Table 1.

DR. COHEN: Yes.

DR. SHANK: I have a very odd suggestion. Maybe we should just eliminate Table 1 for two reasons. One is that the table becomes cumbersome when you have so many studies --

DR. SLAGA: Right.

DR. SHANK: -- and implies equal validity for all of the studies, which is not the case. The other concern about the table is it cannot contain all of the caveats, all of the limitations, et cetera, for all of the studies.

DR. SLAGA: Right.

DR. SHANK: So it makes it very difficult to interpret each -- to evaluate each study. So I don't think the table really helps. And in fact --

DR. SLAGA: I agree with you, Ron.

DR. SHANK: -- it might needs (audio skip).

DR. SLAGA: I think this should be taken out.

DR. SHANK: Sorry, but that's my position.

DR. SLAGA: Yeah. No. I totally agree.

DR. BERGFELD: They have added -- in dermatology at least, what they call the outcome studies, there are methods or ranking them on another column --

DR. SHANK: Yes.

DR. BERGFELD: -- as to the validity of the study. I would find that to be helpful with the listing. I must admit I like the table because it gives me an idea of what's there without all the details. But if I had a ranking scale on the side of it or next to it, that would help me with the interpretation of that and which one I wanted to look at.

DR. COHEN: Yeah. There are standardized rules for developing guidelines of care that rank, you know, placebo-controlled trial, case controlled, cohort studies, and they add an A and a B and a one and -- they rank them, right?

DR. SHANK: I know. I understand. I still don't -- well, it may be helpful to some people, so okay. I think it could be very confusing to most people.

DR. BERGFELD: Or you could add it as an attachment rather than the main document, just as an attachment --

DR. SHANK: Okay.

DR. BERGFELD: -- another way --

DR. SLAGA: That would be good.

DR. BERGFELD: -- of looking at it.

DR. SHANK: That's another way to do it. Good suggestion, Wilma.

MS. FIUME: I do see Thomas has his hand up.

MR. GREMILLION: Thanks, Monice. I had a few questions come up reading this. First, on the study that, Dr. Cohen, you pointed out with the 170,200 women in the Nurse's Health Study, I just wondered -- it was -- looking at the abstract of that study or the writeup of that study, it seemed -- I mean, there were -- it says cumulative dose was positively associated with risk of estrogen receptor negative breast cancer and other breast cancer and ovarian cancer.

And I didn't get that from looking at -- and, you know, some other, you know, results kind of went the other way from the way it's maybe characterized in this. That's on page 56. But I also -- I had more questions about this study on page 6- -- talked about on page 61 with the 46,709 women -- the sister study. And there's just a couple of comments there that didn't seem really supported and kind of threw me.

The first it says, you know, “Limitations of the study design analysis need to be considered before jumping to a general conclusion,” in the middle of the paragraph, “one, because women were recruited to the study because they had a sister with breast cancer, and so conclusions can't be extended to the wider population.” I mean, for me, I see that, and I think well, you know, when they tested the COVID vaccines, they went to people working in emergency rooms. And, I mean, they weren't representative of the entire population, but we still see things -- the statistics of the vaccines being 95 percent effective or whatever it might be.

And it seems that's a pretty reasonable way to get a more statistically relevant result. And I just -- there's not a citation there. And similarly, this third one, the confounding factors warrant further examination it's the (inaudible) regarding endocrine disrupting chemicals, it seems like that could be applied to any number of reviews conducted by CIR.

And then the one in the middle cites a comment -- It was behind a paywall, so I couldn't see it. So maybe it would be -- you know, just kind of indicates that the study hasn't been adjusted for age, and maybe there could be some elaboration on that. That was a little mysterious to me. So I'll stop there.

DR. PETERSON: So I haven't commented yet, and I just want to follow up now because I think it fits well with some of what Thomas said. So overall, I mean, I think this is a tour de force. There's so much data there. But my overall impression of reading, it felt like there was some biases, and I would like to see some edits that would remove -- just sort of make things more unbiased. And so, like, for example, the language “jumping to the conclusion that,” I don't think jumping to the conclusion is appropriate language.

And I thought is Table 1 there because it's just adding the new studies, or is it meant to summarize all the studies in the document? Because it doesn't have all the studies in the document. And so I'm struggling with the value of -- I agree with Ron. I wasn't sure the value of Table 1, but it seems like it was mostly the new studies that were put in.

I felt that all the studies should have the Rollison scale stated for it. There are some new studies, some old studies that have them or don't have them, and I actually think that that's a valuable -- one way that we can actually -- I mean, I think the data are the data, and the data are showing that things are all over the place. But I think the bigger studies are the ones we need to think about being better, but I do think it's important to list them all, that we should have the Rollison scale for all of them, that -- and I would shift the language to being a little less biased because it -- reading it generally I got the impression that all of the positive ones were downplayed and the -- you know, the negative ones which might also have some value -- I mean, have some problems with them also were not -- you weren't -- the negatives of those studies weren't brought out in the same -- kind of the same way.

But I totally agree with everything that Ron and Thomas said. And I think we do need a good characterization of exposure. That hasn't really happened. Some studies start to get at that, but we really need, you know -- there needs to be some stronger assessment of exposure because I think it's going to vary depending on population studied. It may -- risk -- relative risk may vary, you know, on -- there might be -- there seems like there's an -- there could be some issues there that it's because it's associative that it's not showing cause, you know, and it's probably a very complicated relationship between dye exposure and possible cancer risk.

DR. COHEN: Okay. One or two more comments I had. In the WVE study, the metanalysis between hair dye use and the pathogenesis of non-Hodgkin's lymphoma 2019, you know, I found myself going into the source documents and reading them. I don't think that meta-analysis is a study of pathogenesis. It's a study of associations. I don't view looking at case control studies and cohort studies is getting down to the pathogenesis of any disease. It's --

DR. SLAGA: You're breaking up.

DR. COHEN: I think the WVE study, which is a metanalysis, is title pathogenesis, and we describe it as pathogenesis. But I don't think it is. I think it's just a study of associations and odd ratios. It's not a study of pathogenesis. And we shouldn't -- I don't think we should recognize that study as a pathogenesis study.

I mean, it's not designed like that. And they have a conclusion in there that people who frequently use hair dyes or have been using hair dyes for more than 20 years should minimize their exposure to hair dye products to prevent the risk of non-Hodgkin's lymphoma with an odds ratio of 1.4. I found that to be a rather hyperbolic conclusion.

And I guess I'm just sort of echoing what has been said before from the Women's Voice for the Earth. They asked for more -- the term of causal relationship, but I have a hard time with inference of causation and what we've been reviewing. I don't know if we can -- we really can't make that. We can't accommodate that request at this point in time knowing what we know.

DR. PETERSON: Association is not causation. And, you know --

DR. SLAGA: That's right.

DR. COHEN: Yeah. Yeah. Okay.

DR. BERGFELD: Well, Monice, can I ask you a question? The various teams are discussing this. Then we're going to discuss it in panel.

MS. FIUME: Mm-hmm.

DR. BERGFELD: What is the hope for this document? What is the intent? We were supposed to be updating it. Are we going to be making suggestions of changing it or reorganizing it or what?

MS. FIUME: That's going to be up to the panel. The CIR staff tries to bring you the update hopefully every two years. Typically, it was an addition of the new studies that were out there, and then the panel determined whether or not they still felt the same conclusion applied. But if you have changes that you would like to see in the document, then we would just need the feedback on that and how you would like us to proceed with the document.

DR. PETERSON: So is this for more our benefit, or is this some kind of position statement? I mean, I guess I was still wondering the use of the document. Is it for our purposes to sort of understand the epidemiology, or is this a sort of position of the panel that gets projected to the outer world or --

MS. FIUME: Both. So this is to help you understand what's out there, and then there's an epidemiology section in each of the hair dye reports that refers to this resource document and then the overall conclusion of the no association. So if there's changes that you think -- if you don't agree with a conclusion or if you want a different presentation to help you understand what's in there better, we can do that. We just need the guidance as to what you would like to see.

DR. COHEN: So the conclusion is that it does not have sufficient evidence for a causal relationship.

MS. FIUME: Correct.

DR. SLAGA: Correct.

DR. COHEN: That's the conclusion.

DR. PETERSON: And that's --

DR. COHEN: And has that changed in our panel?

DR. SLAGA: No.

DR. PETERSON: No.

DR. SHANK: No. Not at all.

DR. PETERSON: No.

DR. BERGFELD: But I can see reorganizing it and --

DR. PETERSON: Yes.

DR. BERGFELD: -- giving it a ranking -- ranking those that are better studies than others under the various topics.

DR. PETERSON: Yeah. Ones we think that are good science versus -- you know, there's a lot of studies of 25, you know, cases, 25 controls. They're so small. You know, the bigger studies have more validity --

DR. SHANK: Validity.

DR. PETERSON: -- because, you know, basically this is a rare event that's happening. And so, you know, you need the bigger studies to really get at what could be going on. And I think these little studies, while it's worth noting that they're there, you know, I'm not sure that they should be placed on equal footing with the studies where the exposures are much better characterized. There's been attempt to do some kind of dose response relationship based on self-report or whatever.

You know, those -- you know, I get that, you know, there's still all this diversity in hair dyes that people could be using. There's a difference in whether you're dying dark hair or light hair. I mean, there's all this kind of complexity, which totally challenges this kind of -- to do this kind of epidemiological studies.

DR. SLAGA: None of the studies have any dose response.

DR. PETERSON: But I do think that we could --

DR. SLAGA: -- dose response.

DR. PETERSON: Pardon?

DR. SLAGA: None of the studies --

DR. PETERSON: No.

DR. SLAGA: -- have any dose response.

DR. PETERSON: No. But I do think it's --

DR. SLAGA: There are exposure levels that you can deal with, as Ron emphasized.

DR. PETERSON: Yeah.

DR. COHEN: I think, to Lisa's point though, to be fair is that would be pretty hard to do those studies the way we really want to see them --

DR. SLAGA: Right. They're impossible.

DR. COHEN: -- it'd be very difficult, right? There's one, to that point -- I didn't mention it before, but there's one point in that -- one of those studies that talks about pack years of exposure in the hair dye. I think it was a typo because I couldn't find it anywhere else, but it's in the source document. You know, even for cigarettes you can estimate, you know, exposure based on pack years.

DR. PETERSON: Yeah. And it's --

DR. COHEN: This is much more difficult, and we need to sort of take the breaks off and say this is very hard to assess. Not that --

DR. SLAGA: Right.

DR. COHEN: -- it doesn't have it, so it's no good, right?

DR. SLAGA: Right.

DR. BERGFELD: Well, one of the issues here is that the public consumer is worried, and Thomas, you could respond to that. But this is all over the news every time one of these articles comes out.

DR. SLAGA: Oh, yeah. Yes.

DR. BERGFELD: So we have to show some responsibility to this and response.

DR. SLAGA: Yeah. We have to at least show that we're looking at this data --

DR. BERGFELD: Right.

DR. SLAGA: -- very closely.

MR. GREMILLION: Yeah. I think that's absolutely right, and that's why the tone of this and, you know, some of the -- yeah, like Dr. Peterson mentioned, it's important to get it right.

DR. PETERSON: And I think you just, and in being very open. And I do like the ranking of things. So the, you know, here is all the studies, but we put these higher up because for these reasons. And that's why I felt the Rollison scale was actually helpful because, you know, at minimum, the ones that you really are focused on are the ones that have all four of those components to it because it gets closer at sort of what's being evaluated.

When you're comparing all people with all hair dyes, you know, you're probably going to lose any signal for a subset of hair dyes that are things you need to worry about. I mean, it does seem to me there's a difference between people who dyed their hair 40 years ago versus people who are using hair dyes now, you know -- that the product has become much safer than probably it was.

But I do think if we can -- right now, it's just a list, and I think if there's a way of saying this was a well-conducted study -- these are there, but we discount them because they didn't have exposure. That's why I think the Rollison scale is really -- should be there. And the other thing is that the -- not all of the studies report the number of individuals used for that study, the number of cases and controls or prospective study doesn't have -- the number of individuals isn't consistently listed for all the studies. And you really do weigh a study with 25 way different than some with over 2,000.

DR. BERGFELD: Can we get a look at that scale you're referring to? I have not ever seen --

DR. PETERSON: Well, it's in the paper. I mean, it's in the -- actually, I really like the introduction to the --

DR. COHEN: It's estimate of exposure. Lisa, can you apply that to studies, though, that don't have it listed already? I mean, I don't know how --

DR. PETERSON: Well, no, no, no. You have -- so on the background of the document, he talked -- this scale based on Rollison where it assessed ever versus never used got one plus, assessed -- it's on page --

DR. COHEN: Yeah.

DR. PETERSON: -- 55. You know, this scale is used throughout the document but not applied to every study. And I think it's useful because it talks about, you know, really all critical aspects, hair dye, type, color, duration, frequency of use gets at what we, you know -- the closest to what we want to be asking, right?

DR. ZHU: So one thing I want to point out is that some studies don't have Rollison scale because they are meta-analysis, you know --

DR. PETERSON: Oh. Then we should say -- then it should be clear --

DR. ZHU: Yeah.

DR. PETERSON: -- it's a meta-analysis --

DR. ZHU: Basically --

DR. PETERSON: -- and that may be my -- but then it should say the specifics of the meta-analysis. I'm sorry. I might have missed --

DR. SLAGA: Well, it's the meta-analysis that has importance because it takes -- tries to get small numbers and bring a bunch together so that you're looking at them all one time.

DR. COHEN: Yeah.

DR. SLAGA: It has --

DR. BERGFELD: Merit.

DR. SLAGA: -- important aspects. So I -- the meta-analysis studies --

DR. PETERSON: No. There --

DR. SLAGA: -- should be left in.

DR. PETERSON: Yeah. I agree, but sometimes they then remove all of -- it just becomes ever and never. And so, I mean, it is useful to know how the meta-analysis was done. Did they, you know -- because there are going to be meta-analysis where they just look at ever/never and they're not, you know -- there's no breakdown in dye type. And so those are going to be less useful meta-analyses than a meta-analysis that only works with studies that separate these things out.

DR. ZHU: So when meta-analysis is summarized, I think the first sentence has indicated that this is a meta-analysis.

DR. PETERSON: Okay. It was my misunderstanding, probably. I will re-read it with that in mind.

DR. COHEN: So I think we all feel that the additions were relevant. They belong in there. We discussed the wording, and there's consensus over the conclusion.

DR. SLAGA: Right.

DR. PETERSON: Yeah.

DR. COHEN: Okay. And we could discuss this at the group tomorrow about various ways of improving the document, including, I think, the biggest conclusion is maybe looking at the table and ranking them using standardized methodology that are used in other sort of papers that tend to be more like recommendations or standards of care documents. Does that work?

DR. SLAGA: Yeah.

DR. BERGFELD: Yes.

MS. FIUME: And that's --

DR. SHANK: Who's going to do the ranking?

DR. SLAGA: Yeah. And who -- I was going to say who's going to do the ranking, too?

DR. COHEN: Well, you need an epidemiologist who does this kind of thing.

DR. PETERSON: So I can -- I know a number of cancer epidemiologists if you're looking for somebody with specific background in cancer -- applying epidemiological studies to looking at environmental exposures.

DR. COHEN: Okay. I mean, we could pass that along based on the conclusions tomorrow. But when you search this, you could find it online. It's on the CIR website if you want to find -- anyone can find it.

MS. FIUME: And there is a link in all of our hair dye reports to the website. And so I heard you say Table 1 was just getting very, very long. It also sounds that we may be able to break it down into multiple tables based on the type of information, that would also make it --

DR. BERGFELD: Right.

MS. FIUME: -- more useful to the panel?

DR. BERGFELD: Yeah.

DR. SLAGA: Yeah.

DR. PETERSON: Yeah. Like, it'd be nice to have a -- still wouldn't help me -- but, you know, a list of meta-analyses, you know, a list of case control, a list of prospective studies. You know, just some sort of like that. And that, where the --

DR. COHEN: I like that.

DR. PETERSON: -- you know, having the information of the number of, you know, in the case of the meta-analysis, how many different studies were used and, you know, some specific, important details about how to, you know -- how they decided which ones they decided to pull together for the other studies that would be an n-equals of cases and controls or this number perspective study. I mean, those numbers are really helpful. And then getting at this -- you know this -- I really like the ranking that was done in the background with the Rollison scale.

I think that was very helpful for getting a sese of -- because hair dyes are so -- you know, as diverse as tobacco cigarettes are, there's so many different products, you know. They're basically quite similar, but hair dyes are, you know -- depending on the color, it's going to be all over the map. Right?

DR. COHEN: And they're products that I would consider just clinically -- and I'm sure Wilma will comment. They're a little bit less elective than many other cosmetics, right? They are indeed a cosmetic agent, but I think patients find themselves not in the same level of control of use. It's, like, you're either using them or you're not using them as opposed to saying, "I'll use this cosmetic product around my eyes or on my cheeks than another one."

You know, you're sort of limited by permanent hair dye, semi-permanent hair dye, you know, maybe a leave-in product or nothing. Right? So it's great that we have this document, and I really love that not just this but every item that we talk about is just open for everyone to look at. And there's no veil of secrecy whatsoever on this.

MS. FIUME: Total transparency.

DR. SLAGA: As Wilma brought out, it's important that we deal with all these studies. If we leave any out, we will be criticized.

DR. PETERSON: Oh, totally.

DR. SLAGA: As you know.

DR. PETERSON: Totally.

DR. BERGFELD: What we like to do always is to thank the Women's Voices of the Earth because they are always digging, digging, digging and are very helpful --

DR. SLAGA: Right.

DR. BERGFELD: -- and very many times complementary to our work.

DR. COHEN: Very thoughtful analyses, I've got to tell you. Those really detailed letters make you stop and think and interrogate the data more. So I think -- is there any further business for today before tomorrow? You know, I have my work.

DR. BERGFELD: 8:30.

DR. ZHU: So have one question. So do I need to include a meta-analysis into Table 1?

DR. COHEN: I think we're going to talk about how Table 1 will be repurposed tomorrow. So can we table that discussion until tomorrow when we can get a group opinion on what Table 1 should look like?

DR. ZHU: Sure. And then I was wondering how to rank the studies in Table 1, you know -- the standard.

DR. COHEN: That's going to also, I think, be the topic of great discussion tomorrow. Do we do it, how we do it, and who does it?

DR. ZHU: Okay.

DR. PETERSON: But this is really a tour de force, you know. To put everything together in one document like that and summarize everything is really great.

DR. COHEN: Yeah.

DR. BERGFELD: Thank you.

DR. COHEN: Completely agree. And I thank you, Wilma and Monice, for mentoring me through my second meeting.

DR. BERGFELD: Oh, you did great.

MS. FIUME: You did a great job, David.

DR. COHEN: And please, guys, let me know if there's better ways I could prosecute through this list in the future. I'm still new and learning and flexible.

DR. SHANK: You're doing a great job.

MS. FIUME: I thought --

DR. SLAGA: Great job.

MS. FIUME: -- you did a great job.

DR. PETERSON: Thanks, Dave.

DR. COHEN: Thank you, guys.

DR. PETERSON: Really fast learner.

DR. COHEN: It's a privilege working with all of you. I mean that sincerely. All right. So we'll see you tomorrow.

Full Panel - March 12, 2021

DR. COHEN: Okay. So, we had the opportunity to review a resource document on Hair Dye Epidemiology. And, our group wants to first thank, Jinqiu, for powering through a large volume of data and updating this important resource for CIR.

Our team was satisfied with the studies that were chosen, considered them relevant for this document, and agrees with the inclusion in the report. Importantly, we feel the document still substantiates and supports the ultimate findings of the conclusion which we didn't feel needed to change or should change.

Having said that, we received a request from Women's Voices for the Earth about improving Table 1, and we agree with that. We felt that Table 1 has become cumbersome and difficult to interpret, as it list many but not all of the studies within the manuscript. In addition, in the context of the information provided in that table, doesn't easily allow the reader to stratify the size of the population, the quality of the information and analysis, or the list of confounding factors and missing variables.

So, kind of by sharing similar amounts of real estate on the table, the table might have the unintended consequence of leveling the value of the studies despite their various sizes and designs.

We're proposing to break the table into subsections based on the type of study, such as meta-analyses, case controls, etcetera. More importantly, we felt that applying perhaps internationally accepted levels of evidence for studies will allow the reader to more equally prioritize the information they're seeing. This might necessitate the help of a cancer epidemiologist, but I'll give you some examples that are used in guideline formation like, level one is randomized control trials. Level three can include qualitative studies or systemic reviews with or without meta-analyses. And level five can be case reports and literature reviews.

So, that was going to be an important change that we were going to request for Table 1. As for some other requests from the team, I think we're unable to provide statements or conclusions about causation between hair dye use and specific cancers. The evidence is not there and the design of these studies does not provide the information needed or has the necessary rigor with regard to exposure estimates, to allow for a causal statement.

Lastly, we discussed the need for tone in the manuscript when describing the nature of the value of both positive and negative outcomes of the study and we all agreed on the need for improvement in assessing exposure in future studies.

So that's what I would report from our committee.

DR. SLAGA: Nice summary.

DR. BERGFELD: Very nice.

DR. COHEN: I took a lot of notes, Tom, yesterday.

DR. BELSITO: Now, David, I like your suggestions and I think they're all very good. I would just add that, yeah, I think the most concerning thing when I first read it was the incidents of breast cancer in African American women, which was new data.

But, it's very interesting and I appreciate the Council's excellent review (audio skip) in their Wave 3 comments, which I think needs to be brought into the report. Particularly because it goes against almost everything we see where short-term and more recent use was more associated with breast cancer than use pre-1980 which is, you know, seems to be a sort of cutoff where for whatever reason the data started getting softer and softer with any cancer related endpoints.

Also, Paul, made a good point that when we're reporting these studies we tend to give the Rollison score at the end of the study rather than at the beginning of the study. And, he thought that we should consistently move that up, after we talk about the cohort and what the participants were, you know, say give an idea of the Rollison score. So when we're looking at this data, we know how much veracity that there may be in there because it was a more rigorous study versus a very poorly designed, poorly control type of study.

DR. BERGFELD: Well, as I recall, that's a similar presentation that David gave about ranking them according to evidence.

DR. BELSITO: Right. But, when we're actually reviewing the study in the text, so, bring that up to the beginning of the document after we introduce the notion and before we start looking at the data.

DR. PETERSON: I agree with that and I actually think the Rollison scale should be added to the studies where they're looking at genotox (audio skip).

DR. BERGFELD: Okay. Thomas, did you have a question?

MR. GREMILLION: I just wanted to voice support for the idea of having a cancer epidemiologist rank these studies. And, to share my reaction, reading this document, I talked about it with Dr. Cohen's team yesterday. It just seem like there was some discounting in some of the studies, it wasn't really clear why there were some of the comments that were in there. And I think having an expert weigh in on which studies are most reliable and relevant could make this a lot stronger.

DR. BERGFELD: Good comment. Any other comments regarding the hair dye resource document? Bart, do you want to make a comment?

DR. HELDRETH: I don't have any particular comment on it. I know that -- haven't we had an expert epidemiologist out of Italy look at this before?

DR. BELSITO: (Inaudible).

DR. SLAGA: Yeah.

DR. PETERSON: Yeah, I would argue it would be helpful to have somebody who thinks about environmental carcinogenesis with epidemiological type of mind, because I do feel that there's -- you know, I believe that the previous epidemiologist was a dermatologist, but wasn't really -- I couldn't tell a hundred percent what their expertise was.

DR. BERGFELD: They were a cancer specialist.

DR. PETERSON: Oh, okay.

DR. COHEN: I like having someone who's good -- it's an important skill set to do that level of evidence. It's not so easy to do that and to describe it. So, someone who has (audio distorted) epidemiologist that can do that.

DR. BERGFELD: Any other discussion needed here? Jinqiu, you need to say something about your document?

MR. ZHU: So, the studies in Table 1 now are summarized by cancer type. I want to make sure the panel wants to look at the studies summarized by study types? Like the cohort study, case control study, something like that instead of cancer types?

DR. COHEN: You know, I think if there are enough studies by cancer types, we can break down the cancer type by study design. I don't see any reason to stop that part. But we can break down (audio skip) the studies designs.

DR. BERGFELD: Anyone else have a comment about that?

MR. ZHU: Regarding the meta-analysis, what content the Panel wants to be included in Table 1? Meta-analysis covers a lot of information, like the study bias. And, do we need to add each individual information for those studies covered by meta-analysis?

DR. COHEN: You mean listing the references -- or every study in the meta-analysis? I think it will make the table very hard to read, because some of them have a dozen studies in them. I think if you referenced the meta-analysis, I think the reader could easily go and see what studies were in that meta-analysis.

MR. ZHU: Okay. So just the major -- like the result of the meta-analysis, right?

DR. COHEN: Yeah.

MR. ZHU: Okay. How about like the model and the statistical calculation model using the meta-analysis. Any details need to be included?

DR. BERGFELD: Wouldn't that be taken care of by level of evidence, that'd be one of the criteria?

DR. COHEN: It might. I don't know if we need that level of detail in the table. You might put that level of detail in the description in the manuscript, but I don't know if I'd put that in the table.

MR. ZHU: Sure. Because, you know, since that --

DR. SLAGA: I would say it'd make the table too big.

DR. COHEN: Yeah, look, I think the table if we had --

DR. BERGFELD: The table is a directory.

DR. COHEN: Yeah, that's exactly right, but it has a level of evidence for the reader to say, okay there's very high level of evidence, I want to look into that more. I could look into the body of the text or I could go right to the reference.

DR. BERGFELD: Right.

MR. ZHU: Okay. You know, because limitations of some studies have been commented by other papers or other researchers, does those information need to be included in the table as well for the reader?

DR. BERGFELD: No.

MR. ZHU: No?

DR. SLAGA: No.

DR. BERGFELD: No, in the text.

MR. ZHU: Okay. Okay, I'm good.

DR. BERGFELD: Okay? Bart, do we need to do anything else with all these recommendations?

DR. HELDRETH: No, that's perfectly fine as long as Jinqiu has everything he needs. We'll take a look at editing this document, seeing if we can get some recommendations on the value of each study from an external expert, and get back to the panel with that new iteration sometime in the not too distant future.

DR. BERGFELD: Okay.