National Toxicology Program
Board of Scientific Counselors
Technical Reports Review Subcommittee

February 17-18, 2004

NIEHS, Research Triangle Park, NC

Summary Minutes

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Attendees

Members:
Mary Anna Thrall (chair)
Larry Andrews
Diane Birt
Kim Boekelheide
Michael Elwell
Thomas Gasiewicz
Shuk-Mei Ho
James Klaunig
Charlene McQueen
Walter Piegorsch
Stephen Roberts
Richard Storer
Mary Vore

Members Absent:
John Giesy, Jr.
Cheryl Lyn Walker

***Ad hoc* Reviewers:**
George Bailey
Jerry "Mac" Law

NIEHS Attendees:
Gary Boorman
Amy Brix
Rajendra Chhabra
Teddy Devereux
Adriana Doi
Skip Eastin
Larry Fischer
Steven Kleeberger
Dave Malarkey
Jeanelle Martinez
Abraham Nyska
Joe Roycroft
William Schrader
Cynthia Smith
Hideko Sone
Fernando Suarez
Mary Ellen Sutphin
Kris Thayer
Hiro Toyoshiba
Molly Vallant
Michael Wyde

Agency Attendees:
William Allaben, FDA
Neil Allison, EPL
Frederick A. Beland, NCTR
Sandra Culp, NCTR/FDA
Kevin Greenlees, FDA
Mark Toraason, NIOSH

Public Attendees:
Orn Adalsteinsson, Arkion Life Sciences
Andrew Ballard, BNA, Inc.
S. Bisch, Dynamic
Ken Bollinger, Airepel
Todd Bunnell, SePRO Corporation
Byron Butterworth, Butterworth Consulting
Patrick Crockett, Constella
Tom Deardorft, Arkion Life Sciences
Michael Easterling, Constella
John Festa, American Forest and Paper Association
Steve Graver, Battelle
Milton Hejtmancik, Battelle
Michael Jokinen, Pathology Associates
Paul Mellick, Charles River Labs
Thomas Starr, TBS Associates
Camille Wallwork, Constella
Chris Widrig, Airepel/ Arkion Life Sciences

Peer Review Meeting- February 17, 2004

The meeting began at 8:30 a.m. on February 17, 2004, in the Rodbell Auditorium of the David P. Rall Building, National Institute of Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina.

Dr. Nigel Walker, NIEHS, presented the background, design, and goals of a series of NTP studies on the Toxic Equivalency Factor (TEF) evaluation of mixtures of dioxin-like compounds (dioxins, polychlorinated biphenyls [PCB's] and furans). Dr. James R. Hailey, NIEHS, then described the pathology review process for these studies and presented examples of the characteristic spectrum of neoplastic and nonneoplastic lesions in the liver and lung in animals exposed to these compounds.

2,3,7,8-Tetrachlorobenzo-*p*-dioxin (TCDD)

Dr. Walker introduced the toxicology and carcinogenesis studies of 2,3,7,8-tetrachlorobenzo-*p*-dioxin (TCDD) by noting that this chemical is the benchmark reference chemical for the TEF methodology. He described the study design and the spectrum of hormonal and histopathologic alterations seen in the liver, lung, oral mucosa and pancreas, as well as nonneoplastic lesions in a variety of other tissues. The proposed conclusions were:

> Under the conditions of this 2-year gavage study there was *clear evidence of carcinogenic activity* of TCDD in female Harlan Sprague-Dawley rats based on increased incidences of cholangiocarcinoma and hepatocellular adenoma of the liver, cystic keratinizing epithelioma of the lung, and gingival squamous cell carcinoma of the oral mucosa. The increased incidence of squamous cell carcinoma of the uterus was also considered to be related to TCDD administration. The marginally increased incidences of pancreatic acinar neoplasms and occurrences of hepatocholangioma and cholangioma of the liver may have been related to TCDD administration.

TCDD administration caused increased incidences of nonneoplastic lesions of the liver, lung, oral mucosa, pancreas, thymus, adrenal cortex, heart, clitoral gland, kidney, forestomach, and thyroid gland in female rats.

Dr. Michael Elwell, the first principal reviewer, said the study was well designed and included a number of useful mechanistic studies. He suggested inclusion of inflammation of the mesenteric artery as another nonneoplastic effect in the conclusions.

Dr. Thomas Gasiewicz, the second principal reviewer, suggested that references to increases or decreases in lesion incidence implied statistical significant differences that were not statistically significant and should be so specified. He inquired about variations in control values for thyroid hormones and the bromodeoxyuridine (BrdU) labeling index at different time points and whether more quantitative criteria could be assigned for severity grades for nonneoplastic lesions. He also questioned whether inclusion of squamous cell carcinoma of the uterus in one dose group was treatment-related and whether this statement should be included in the conclusion.

Dr. Kim Boekelheide, the third principal reviewer, also suggested attempts to quantify the diagnostic criteria for histopathologic diagnoses. He asked whether the scientists had considered any molecular approaches to distinguish between hyperplasia and adenoma and Dr. Walker answered that they had tried staining for placental glutathione-S-transferase (PGST) but this marker was not useful in this situation. He also questioned the approach used to classify a lesion as minimal, mild, moderate and severe. Dr. Hailey responded that it is relatively easy to identify a minimal and severe response, but the intermediate classifications are a little more subjective. Dr. Boekelheide appealed to the NTP scientists to quantify their diagnostic categories and define them as clearly as possible as he envisaged that these reports on TCDD and PCB's would be used in the future as the benchmark description of the pathology from animals treated with dioxin and polychlorinated biphenyls.

Dr. Walker explained that the measurements for clinical chemistry parameters were performed sequentially at the time of measurement, with emphasis on comparison between dose groups; thus, differences between different time points might be artefactual. Differences in water consumption could also have been a factor.

Dr. Walker said the carcinomas of the uterus were also observed in the stop study, which lent credence that these lesions were chemically-induced. Dr. Elwell added that the occurrence of five such tumors in one dose group seemed sufficiently significant, particularly since another database of industry studies reported only two such tumors in 900 historical control female Sprague-Dawley rats. Dr. Abraham Nyska, NIEHS, said expanded diagnostic criteria for nonneoplastic lesions would be included in the final document.

Dr. William Allaben, NCTR, inquired about the choice of corn oil as the gavage vehicle. Dr. Walker replied that corn oil was used to permit comparison with other studies in the literature, which used that route. Dr. Thrall suggested including bone marrow smears along with histopathology routinely in studies of chemicals associated with lymphoproliferative or myeloproliferative diseases.

Dr. Elwell moved that the conclusions be accepted as written, upon the addition to the conclusions of inflammation of the mesenteric artery and mention of ovarian atrophy in the text of the abstract. Dr. Boekelheide seconded the motion, which was approved unanimously with 12 yes votes.

3,3',4,4',5-Pentachlorobiphenyl (PCB 126)

Dr. Nigel Walker, NIEHS, introduced the toxicology and carcinogenesis studies of 3,3',4,4',5-pentachlorobiphenyl (PCB 126) by noting that of the dioxin-like PCBs, it is the most potent and is used as a reference compound in developing potency factors. He described the study design, the spectrum of lesions in the liver, lung and oral mucosa and a variety of nonneoplastic lesions. The proposed conclusions were:

> Under the conditions of this 2-year gavage study there was *clear evidence of carcinogenic activity* of PCB 126 in female Harlan Sprague-Dawley rats based on increased incidences of cholangiocarcinomas of the liver and squamous neoplasms of the lung (cystic keratinizing epithelioma and squamous cell carcinoma) and gingival squamous cell carcinoma of the oral mucosa. Hepatocellular adenoma and hepatocholangioma of the liver were also considered to be related to the administration of PCB 126. Neoplasms of the adrenal cortex and cholangioma of the liver may have been related to the administration of PCB 126.

PCB 126 administration caused increased incidences of nonneoplastic lesions of the liver, lung, adrenal cortex, pancreas, kidney, heart, thyroid gland, thymus, spleen, clitoral gland, and mesenteric artery in female rats.

Dr. James Klaunig, the first principal reviewer, felt the study was well designed and agreed with the conclusions. He inquired about the cause of apparent iron accumulation in the Kupffer cells. Dr. Walker answered that this was likely caused by alteration in porphyrin metabolism.

Dr. Walter Piegorsch, the second principal reviewer, also agreed with the conclusions.

Dr. Richard Storer, the third principal reviewer, said the study was well designed and he agreed with the conclusions. He suggested adding a listing of the outside grantees who obtained materials from these studies to facilitate referencing their additional research.

Dr. Klaunig moved, and Dr. Piegorsch seconded, that the conclusions be accepted as written. The motion was passed unanimously with 12 yes votes.

2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)

Dr. Nigel Walker, NIEHS, introduced the toxicology and carcinogenesis studies of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF), by noting it is the most potent polychlorinated dibenzofuran in the Toxic Equivalency Factor scheme. He described the study design, the reduction of body weights, the spectra of effects in the liver, lung, oral mucosa, uterus, and pancreas and a variety of nonneoplastic lesions. The proposed conclusions were:

> Under the conditions of this 2-year gavage study, there was *some evidence of carcinogenic activity* of PeCDF in female Harlan Sprague-Dawley rats, based on increased incidences of hepatocellular adenoma and cholangiocarcinoma of the liver and gingival squamous cell carcinoma of the oral mucosa. Occurrences of cystic

> keratinizing epithelioma of the lung, neoplasms of the pancreatic acinus, and carcinoma of the uterus may have been related to administration of PeCDF.
>
> PeCDF administration caused increased incidences of nonneoplastic lesions of the liver, oral mucosa, uterus, lung, pancreas, thyroid gland, thymus, adrenal cortex, kidney, heart, and forestomach in female rats.

Dr. Shuk-Mei Ho, the first principal reviewer, said the study was designed and described well and she agreed with the conclusions. She emphasized that this chemical is nonmutagenic and suggested the possibility that besides interacting with the aryl hydrocarbon hydroxylase (Ah) receptor it might also suppress an immune response. She thought the interplay of several mechanisms might explain the nonlinearity of the proliferative responses.

Dr. McQueen, the second principal reviewer, also agreed with the conclusions.

Dr. Birt, the third principal reviewer, agreed with the conclusions and suggested expanding the description of the diagnostic criteria for pathological changes.

Dr. Walker agreed the chemical is a nongenotoxic carcinogen and noted that frequently the liver proliferative response in these laboratory animals were more skewed than normally distributed.

Dr. Ho moved, and Dr. McQueen seconded, that the conclusions be accepted as written. The motion was passed unanimously with 12 yes votes.

Dioxin Mixture (TCDD, PeCDF, PCB 126)

Dr. Nigel Walker, NIEHS, introduced the toxicology and carcinogenicity study of a mixture of TCDD, PeCDF, and PCB 126 by noting that the primary purpose of the study was to test the question of dose additivity in the toxic response. He noted that these three chemicals together contribute 40% of the total dioxin toxic equivalence to which humans are exposed. He described the study design and the responses in the liver, lung, adrenal cortex, and pancreas and a variety of nonneoplastic effects. The proposed conclusions were:

> Under the conditions of this 2-year gavage study, there was *clear evidence of carcinogenic activity* of the mixture of TCDD, PeCDF, and PCB 126 in female Harlan Sprague-Dawley rats based on increased incidences of cholangiocarcinoma and hepatocellular adenoma of the liver and cystic keratinizing epithelioma of the lung. Neoplasms of the pancreatic acinus may have been related to administration of the mixture of TCDD, PeCDF, and PCB 126.
>
> Administration of the mixture of TCDD, PeCDF, and PCB 126 caused increased incidences of nonneoplastic lesions of the liver, lung, pancreas, adrenal cortex, oral mucosa, uterus, thymus, ovary, kidney, heart, bone marrow, urinary bladder, mesenteric artery, and thyroid gland in female rats.

Dr. Roberts, the first principal reviewer, felt the study was rationally designed and well conducted. Given the large number of sites affected, he suggested adding subheadings to the discussion section.

Dr. Vore, the second principal reviewer, also felt the study was well conducted and agreed with the conclusions. She inquired if dose additivity was expected.

Dr. Andrews, the third principal reviewer, also agreed with the conclusions. He sought some discussion about the issue of using a rodent bioassay designed to test for complete carcinogens to assess the promotional effects of dioxins. He suggested some additional discussion on the timing of thyroid function in the rat, to help clarify the relative increases and decreases in thyroid hormone levels at the interim sacrifice points.

Dr. Walker said the question of dose additivity would be explored once the entire set of TEF studies are complete. He explained that the chemicals were tested in complete cancer studies because of criticisms that earlier promotional studies were not complete. While promotion may be the major effect of the dioxins, it may not be the only mechanism operating. Dr. C. Portier, NIEHS, emphasized that the program was careful to attribute promotion effects just to results of properly controlled initiation-promotion studies; otherwise, as here, "nongenotoxic mechanism" would be a better characterization of the effect. Dr. Klaunig and Dr. Andrews agreed.

Dr. Roberts moved, and Dr. Vore seconded, that the conclusions be accepted as written. The motion was passed unanimously with 12 yes votes.

Malachite Green Chloride and Leucomalachite Green

Dr. Sandra Culp, NCTR, introduced the toxicology and carcinogenesis studies of malachite green chloride and leucomalachite green by describing the use of the chemicals as an antifungal agent in fisheries, the study design and dose setting, and the data on body weight, blood parameters, and lesions of the liver, mammary gland, thyroid gland, and testes. The proposed conclusions were:

> Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity* of malachite green chloride in female F344/N rats based on the occurrence of thyroid gland follicular cell adenoma or carcinoma (combined) and marginal increases in hepatocellular adenoma and mammary gland carcinoma in exposed rats. There was *no evidence of carcinogenic activity* of malachite green chloride in female B6C3F_1 mice exposed to 100, 225, or 450 ppm.
>
> Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity* of leucomalachite green in male F344/N rats based on an increase in interstitial cell adenoma of the testes and the occurrence of thyroid gland follicular cell adenoma or carcinoma (combined) in exposed rats. There was
>
> *equivocal evidence of carcinogenic activity* of leucomalachite green in female F344/N rats based on marginally increased incidences of mammary gland adenoma or carcinoma (combined) and hepatocellular adenoma, and the occurrence of thyroid gland follicular cell adenoma or carcinoma (combined) in exposed rats. There was *some evidence of carcinogenic activity* of leucomalachite green in female B6C3F_1 mice based on an increase in hepatocellular adenoma or carcinoma (combined).

> Exposure to malachite green chloride in feed resulted in nonneoplastic lesions in the thyroid gland and liver of female rats and the urinary bladder and liver of female mice. Exposure to leucomalachite green in feed resulted in nonneoplastic lesions in the thyroid gland and liver of male and female rats and the urinary bladder of female mice.
>
> Decreased incidences of mononuclear cell leukemia in female F344/N rats were attributed to malachite green chloride exposure. Decreased incidences of mononuclear cell leukemia in male and female F344/N rats and pituitary gland adenomas in male rats were attributed to leucomalachite green exposure.

Dr. Storer, the first principal reviewer, felt the genotoxicity, DNA adduct, and transgenic mouse results should be presented more prominently. He also requested more discussion of the alteration in thyroid hormone levels.

Dr. Elwell, the second principal reviewer, thought the dose selection rationale could be clarified. He questioned the justification for combining mammary gland adenomas and carcinomas, while omitting the inclusion of fibroadenomas, to obtain a combined count of tumors as evidence of an equivocal response. He also thought the lymphocytic infiltration noted in the malachite green study is a common background lesion. He asked for more explanation of the interpretation of retinal degeneration and for some discussion comparing these compounds with gentian violet. Regarding the conclusions, he suggested deleting any mention of lymphocytic infiltration in mice in the malachite green study and the mammary gland tumors in female rats in the leucomalachite green study.

Dr. Roberts, the third principal reviewer, felt more justification was needed for the dose selection. He thought the retinal degeneration is potentially compound-related. He also questioned the study design that focused mainly on female animals, based on four-week study results.

Dr. Culp agreed to expand the study design, and dose selection rationale and the genetic toxicology section. She also agreed to remove the lymphocytic infiltration from the abstract table.

Dr. Paul Mellick, NCTR, agreed that combining fibroadenomas with the other mammary gland tumors would eliminate any effect. Dr. John Bucher, NIEHS, said the link between carcinomas and adenomas might be more persuasive than the link between carcinomas and fibroadenomas, and noted that these tumors occurred despite lower body weights.

Dr. Culp said the retinal degeneration was central rather than peripheral and was not likely due to fluorescent lighting because the cage placements were rotated. She defended the decision to use primarily female animals, noting that females had more severe effects in the range-finding studies.
Dr. Fred Beland, NCTR, added that the lower background rates for liver tumors in females enhanced the ability to discern small increases.

Dr. Klaunig inquired about the liver adenomas in female rats for both chemicals. Dr. Culp said that although the marginal increases were not statistically significant, the incidences were outside the historical control ranges. Dr. Beland added that the genotoxicity data supported a genotoxic mechanism in the mouse liver while the response in the rat liver was equivocal.

Dr. Storer moved that the conclusions for the malachite green study be accepted as written, with the exception that lymphocytic infiltration of the liver be removed from the list of nonneoplastic lesions for female rats. Dr. Elwell seconded the motion. Dr. Piegorsch asked for the reasons supporting the inclusion of thyroid, liver, and mammary tumors as equivocal responses for female rats. Dr. Elwell explained that for each site, there was an occurrence of a few tumors; these marginal increases did not achieve statistical significance, but did exceed the observed historical control ranges. Dr. Andrews added that since the animals might have been able to tolerate even higher doses, noting these equivocal responses is appropriate. The motion was approved with 10 yes votes and two no votes (Klaunig and Piegorsch).

Dr. Elwell suggested that the conclusions for the leucomalachite green study be accepted as written with the exception that mammary gland tumors be removed from the list of lesions supporting equivocal evidence in female rats. There was some discussion about which types of mammary gland tumors could most appropriately be combined for statistical analyses. Dr. J. Richard Hailey, NIEHS, said progression from benign to malignant tumors is less common in the mammary gland than at some other sites.

Dr. Storer moved to accept the conclusions as written, including the mammary gland lesions. The motion failed for lack of a second.

Dr. Storer then moved to accept the motion as written with the mammary gland tumors for female rats deleted. Dr. Elwell seconded the motion. Dr. Piegorsch inquired whether the thyroid gland neoplasms should also be removed from the conclusion. Dr. Storer replied that these are very uncommon tumors and there is supporting biologic plausibility based on the disturbance of thyroid hormone homeostasis. Dr. Storer also noted that in support of retaining the liver lesions in the conclusion, only one adenoma had been seen in the control groups for six other studies. The motion was approved with 11 yes votes and 1 no vote (Klaunig).

Anthraquinone

The draft NTP Technical Report on anthraquinone was previously peer reviewed by the Subcommittee in May 1999. Subsequent to that peer review, the anthraquinone tested was found to contain a 0.1% contaminant. As a result, additional mutagenicity and metabolism studies were conducted and the findings from those studies are included in the revised draft report reviewed at this meeting. The Subcommittee evaluated the results from these follow-up studies, and used that information to re-examine the carcinogenicity findings from the 2-year studies and to make a recommendation on the carcinogenicity of anthraquinone. Dr. Rick Irwin, NIEHS, introduced the rereview of the toxicology and carcinogenesis studies of anthraquinone, by presenting the conclusions that had been approved at the May 21, 1999 peer review meeting. Following the peer review, the NTP was informed that the 0.1% impurity was likely 9-nitroanthracene, a bacterial mutagen. Dr. Irwin presented the results of subsequent studies to characterize the 0.1% contaminant and investigate the mutagenicity of anthraquinone, 9-nitroanthracene, and the urinary metabolites of anthraquinone. For the latter study, samples of anthraquinone produced by all three synthetic processes were compared. The major urinary metabolites were 1-hydroxyanthraquinone and 2-hydroxyanthraquinone.

Dr. Irwin confirmed that purified anthraquinone is not a mutagen itself, nor is the metabolite 1-

hydroxyanthraquinone, although the latter is a rodent carcinogen. The major metabolite, 2-hydroxyanthraquinone, was found to be a mutagen in the Ames assays in *Salmonella typhimurium* TA 98 strain, producing several -fold more revertants per microgram than 9-nitroanthracene. The amounts of 2-hydroxyanthraquinone measured in male rat urine were greater than the levels of the 0.1% 9-nitroanthracene impurity even if the latter were 100% bioavailable. Dr. Irwin concluded that if the observed carcinogenicity of anthraquinone occurs through the action of a mutagen, the metabolite 2-hydroxyanthrquinone could account for the observed pattern of tumorigenicity. He was of the opinion that low exposure levels, bioavailability, and relative mutagenicity make it unlikely that 9-nitroanthracene contributed significantly to the results of the carcinogenicity studies.

Regarding the measured purity of the study materials, Dr. Cynthia Smith, NIEHS, explained that all purity measurements are relative and rely on the parameter being measured, e.g. total mass of carbon hitting a detector or absorption at a particular wavelength by chromophores. For this particular study, the gas chromatography measure was considered most representative.

Public comments

Dr. Bryon Butterworth, representing Arkion Life Sciences, asserted that the material used in the NTP studies contained 0.6% impurities and that they were mutagenic. He distinguished between material produced by different synthetic processes and that produced by oxidation of anthracene and suggested that all the observed carcinogenic activity in the NTP bioassay might have been due to the impurity. He further claimed that the mutagenicity attributed to 2-hydroxyanthraquinone was also due to impurities.

Dr. Boekelheide asked Dr. Butterworth which analytic method Arkion used to obtain the higher measure of impurity. Dr. Butterworth replied that the samples were subjected to a recrystallization process to remove the anthraquinone and the resultant supernatant was then analyzed. Dr. Orn Adalsteinsson, Arkion Life Sciences, said a variety of analytic measures were used at three different laboratories, and by comparing the location of the various peaks on the chromatogram against reference standards, they were able to calculate the concentration of the impurities. Dr. Smith asked which of the several methods was used to yield the impurity value of 0.6% and how could one have reference standards for unidentified organics. Dr. Adalsteinsson said high performance liquid chromatography (HPLC) was the method used for quantification.

Dr. Charlene McQueen, the first principal reviewer, thought the issue of metabolism was addressed in the presentation and the question of the impurity characterization was described well in the text of the report, but not in the abstract. She suggested that both the impurities and the metabolites could be contributors to the overall carcinogenicity.
Dr. Ho, the second principal reviewer, felt she could agree with the study conclusions.

Dr. Andrews, the third principal reviewer, thought the explanation of attributing the carcinogenicity to the metabolite 2-hydroxyanthraquinone was plausible. He thought that the argument could be strengthened by a fuller metabolism study and clarification of the mutagenicity of the metabolites.

Dr. Irwin noted research from NCTR indicating that purified 9-nitroanthracene is actually a very weak mutagen, possibly nonmutagenic. He added that 2-hydroxyanthraquinone is mutagenic, as Dr. Butterworth had shown. As a metabolite, it would be present in much larger quantities than any of

the putative impurities and simply could not be dismissed as a contributor to the observed tumors. Dr. Irwin also observed that the reagent grade material used in the NTP study was the highest commercial grade material available at the time. Dr. Butterworth disagreed and said that in recent years the industry has used material synthesized by other pathways.

Dr. Christopher Portier, NIEHS, noted that the class of mutagens identified as other impurities in the test material are potent point-of-contact carcinogens. However, in the present study no forestomach tumors, which would be expected after oral exposure to such chemicals, were observed. Dr. Storer said such chemicals as benzo-[*a]*-pyrene still require activation. He added that the Technical Report contained a great deal of valid toxicology and pathology work and the key question is the proper way to define the material relative to the commercial product. Dr. Butterworth suggested calling it "anthracene-based anthraquinone".

Drs. McQueen and Roberts agreed that the studies were valid tests of the material tested and the issue is how to designate the material. Dr. Boekelheide disagreed noting that probably no NTP studies have ever been conducted on an absolutely pure chemical and that the test material is representative of commercially produced anthraquinone. He foresaw the danger of creating a pathway to challenge any study result. He also was concerned about narrowly limiting the conclusion by calling the test material something other than anthraquinone and thus freeing the commercial material from public health concern. Dr. Portier said the material tested by the NTP was 99.9% anthraquinone, and the argument being presented is a theoretical hypothesis that the observed carcinogenicity resulted instead from an untested, potentially genotoxic compound. Dr. Bucher reminded the panel that the report is a study on anthraquinone, and the conclusions were not based on establishing whether the 2-hydroxyanthraquinone is a mutagen or the causative mechanism.

Dr. Adalsteinsson again claimed that the impurity was 0.6% rather than 0.1%. Dr. Leo T. Burka, NIEHS, suggested that removing the anthraquinone by recrystallization might have concentrated the contaminants. Dr. McQueen felt that whether the chemical was 99.9% or 99.4% pure was not a major issue, as either way an impurity was present and efforts were made to assess its contribution.

Dr. Ho said she felt comfortable calling the test compound just anthraquinone and cited two examples of other chemicals with strong carcinogenic or protective activities where the active agents were their metabolites. Dr. Storer said that even if the test material is called anthracene-derived anthraquinone, the burden of proof would remain on industry to prove that anthraquinone is safe. Dr. Andrews felt it is possible to clarify the origin of the material in the text of the report without changing the title. Dr. Vore agreed. Dr. Boekelheide questioned whether the regulatory burden would remain if the name of the test chemical were modified. Drs. Portier and Allaben noted that the regulatory implications were beyond the purview of this review and the focus should be on scientific accuracy.

Dr. McQueen moved that the conclusions be accepted as written, with the amendment that the test material be called anthracene-derived anthraquinone in the title and in a defining sentence at the start of the conclusion. Dr. Storer seconded the motion. The vote was tied, with six members (Andrews, Klaunig, McQueen, Piegorsch, Roberts, and Storer) voting yes and six (Birt, Boekelheide, Elwell, Gasiewicz, Ho, and Vore) voting no. Dr. Thrall, as chair, voted in favor of the motion and the motion carried.

Peer Review meeting- February 18, 2004

The meeting began at 8:30 a.m. on February 18, 2004 in the Rodbell Auditorium of the David P. Rall Building, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The purpose of this meeting was the review a draft of a NTP Technical Report describing the carcinogenesis studies of 2,2-bis(bromomethyl)-1,3-propanediol, nitromethane, and 1,2,3-trichloropropane in two fish species (medaka and guppies). Members of the subcommittee and two *ad hoc* reviewers, Drs. George Bailey and Jerry "Mac" Law, were present.

Overview of Fish Studies

Dr. George Bailey, Oregon State University, presented an overview of the history of carcinogenesis research in fish models. Dr. Bailey summarized the results of a variety of studies in different fish species, noting that the response to carcinogens varies among species. Among the advantages of fish studies compared with rodents is the lower cost and smaller space requirements per individual, permitting studies with large sample numbers per dose group. Among the drawbacks is the absence of certain organ systems in fish that are present in mammalian species.

2,2-bis(Bromomethyl)-1,3-propanediol, Nitromethane, and 1,2,3-Trichloropropane

Dr. Gary Boorman, NIEHS, introduced the carcinogenesis studies of three chemicals (2,2-bis(bromomethyl)-1,3-propanediol, nitromethane, and 1,2,3-trichloropropane) in two species of fish, medaka (*Oryzias latipes*) and guppy (*Poecilia reticulata*) by explaining that the intent of these studies was to test the feasibility of the fish models. The chosen test chemicals were three chemicals characterized as carcinogenic in NTP rodent studies. Dr. Boorman described the study design, the exposure facility, and the pathology review procedure. For each chemical study, he discussed survival of the two fish species and compared the responses in the two fish species with the results of the rodent studies.

For these studies the conclusions were not framed in the standard Levels of Evidence categories. The proposed conclusions were:

> Under the conditions of these waterborne studies, 2,2-bis(bromomethyl)-1,3-propanediol at concentrations of up to 150 mg/L for 16 months was considered carcinogenic for male guppies based on increased incidences of hepatocellular adenomas or carcinomas. The study in female guppies was considered inadequate based on reduced survival. Under the conditions of these waterborne studies, 2,2-bis(bromomethyl)-1,3-propanediol at concentrations of up to 150 mg/L for 14 months was considered carcinogenic for male medaka based on increased incidences of hepatocellular adenomas or carcinomas. The study in female medaka was considered negative.
>
> Under the conditions of these waterborne studies, the study of nitromethane in male guppies was considered inadequate based on reduced survival. The study in female guppies at concentrations up to 70 mg/L for 16 months was considered negative. Under the conditions of these waterborne studies, the study of nitromethane at concentrations of up to 40 mg/L for 13 months was considered equivocal for male

medaka based on the occurrence of cholangiomas or cholangiocarcinomas. The study in female medaka was considered negative.

Under the conditions of these waterborne studies, 1,2,3-trichloropropane at concentrations of up to 18 mg/L for 16 months was considered carcinogenic for male and female guppies, based on increased incidences of a variety of liver neoplasms. Under the conditions of these waterborne studies, 1,2,3-trichloropropane at concentrations of up to 18 mg/L for 13 months was considered carcinogenic for male and female medaka, based on increased incidences of a variety of liver neoplasms and papillary adenoma of the gallbladder.

Dr. Boorman noted that the performance of the studies was not as inexpensive as anticipated, the models were less sensitive than rodent studies, as gauged by the number of sites at which responses were elicited, and interpretation of the findings was limited by lack of time-to-tumor data and decreased survival of some of the fish.

Dr. Boekelheide, the first principal reviewer, had several concerns about the technical limitations of these studies: the fish were not initially sexed and were potentially reproducing, their sizes varied with the number of fish per tank, and the occurrence of algal blooms and a background infection of granulomata presented other confounders. He did concur with the proposed concluding assessments.

Dr. Piegorsch, the second principal reviewer, applauded the effort to explore new test systems, but agreed that many design and control issues would have to be resolved. For the specifics of the studies at hand, he noted a number of cases where very low tumor incidences were being presented as supporting an equivocal conclusion. He inquired about the inclusion of stop-study data and discussed a fundamental flaw of fish dying and being cannibalized resulting in a loss of key data.

Dr. Klaunig, the third principal reviewer, also mentioned the issues of survival and husbandry and was concerned about the possibility of fish dying from lesions and then disappearing. He was of the opinion that some of the larger fish species might offer better chances to observe tumors and particularly tumor multiplicity.

Dr. Bailey said doing sex determinations at the start of a study would not be possible, but he did not consider that a severe limitation. Overall, he felt optimistic about the prospects for fish research based on the experience of these studies.

Dr. Jerry "Mac" Law, North Carolina State University, was the second *ad hoc* reviewer. Dr. Law suggested that fish studies did offer some economy-of-scale for tests involving very large numbers of animals. He was concerned about the extent of the granuloma infection and the effects of the resultant inflammation. He felt that the pathology diagnoses could have been undertaken more rapidly with fewer slides per fish.

Dr. Boorman acknowledged the recommendations of the reviewers and suggested that this report be part of the Technical Report series rather than a summary article, to permit full reporting of the study details and lessons learned. Dr. Hailey indicated that stop-study data are becoming a regular part of NTP studies.

Dr. Bailey pointed out that no false positives have ever been reported in fish studies. He also mentioned that for larger fish like trout, the survival rates are much higher.

Dr. Boekelheide moved, and Dr. Klaunig seconded, that the conclusions be accepted as written. Dr. Piegorsch offered an amendment that the conclusion for nitromethane in male medaka be changed from equivocal to negative. Dr. Birt seconded the amendment. The amendment was approved with seven yes votes (Birt, Boekelheide, Klaunig, Piegorsch, Roberts, Storer, Vore), three no votes (Andrews, Elwell, Ho), and two absent (Gasiewicz, McQueen). The overall conclusion, as amended, was approved with 8 yes votes (Birt, Boekelheide, Ho, Klaunig, Piegorsch, Roberts, Storer, Vore), two no votes (Andrews, Elwell) and two absent (Gasiewicz, McQueen).

In further discussion, Dr. Portier argued for presenting these studies in the existing Technical Report series rather than creating a special report series for every different study design. Dr. Klaunig said fish are a valid model for carcinogenicity. Dr. Andrews recalled that discussions about the vision for the future of the program included exploring different and predictive models and this is one such attempt. Dr. Storer distinguished the fish studies from the transgenic mouse studies, noting that some of the latter studies might be characterized as a reporter gene model whereas for the fish studies cancer is the endpoint. Dr. Piegorsch noted that at the beginning of the rodent bioassay series many of the technical and analytic refinements had not yet been developed. Dr. Ho favored keeping this report in the Technical Report series because fish have long been used as a model for carcinogenesis.

Drs. Storer and Klaunig noted that most of the fish studies involve testing carcinogens rather than non-carcinogens. Dr. Boekelheide said if more studies were to be performed using fish models, then a major investment would be required. Dr. Portier felt most confounders could be overcome, but the key question to be resolved is the problem of loss of fish (and data) during a study. Dr. Bailey felt that this issue could be resolved by choosing the appropriate species and husbandry system. Drs. Birt and Storer felt that these models could be promising for low-dose extrapolation studies that require very large numbers of animals.

Before the meeting adjourned, Dr. Roberts requested time at a future meeting for discussion of what circumstances would cause the presence of an impurity in a test material to affect the framing of a study's conclusions. He asked for an agency presentation as to how this issue has been dealt with in the past.

requires evidence from studies of humans. This can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues from humans exposed to the substance in question and useful for evaluating whether a relevant cancer mechanism is operating in people.

There have also been some misunderstandings regarding the application of the final paragraph of the criteria which begins, "Conclusions regarding carcinogenicity in humans or experimental animals* * *" Since these criteria were first published on September 26, 1996 (61 FR 50499–50500), the paragraph has applied to both the "known to be human carcinogen" and the "reasonably anticipated to be human carcinogen" categories and will continue to apply (64 FR 19188, April 19, 1999).

[FR Doc. 03–30122 Filed 12–2–03; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program (NTP) Board of Scientific Counselors Technical Reports Review Subcommittee Meeting; Review of Draft NTP Technical Reports

Pursuant to Public Law 92–463, notice is hereby given of the next meeting of the NTP Board of Scientific Counselors Technical Reports Review Subcommittee ("the Subcommittee") on February 17–18, 2004, in the Rodbell Auditorium, Rall Building at the National Institute of Environmental Health Sciences, 111 T. W. Alexander Drive, Research Triangle Park, NC 27709. The meeting will begin at 8:30 a.m.

Agenda

The primary agenda topic is the peer review of seven draft NTP Technical Reports of rodent toxicology and carcinogenesis studies conducted by the NTP. This includes the re-review of the NTP Draft Technical Report on Anthraquinone (TR #494), which was originally reviewed in May 1999. The reports are listed in the table below in the tentative order of their review.

The agenda and roster of the Subcommittee members will be available prior to the meeting on the NTP homepage at *http://ntp-server.niehs.nih.gov/*(see What's New?) and upon request to the NTP Executive Secretary, Dr. Barbara S. Shane (P.O. Box 12233, 111 T.W. Alexander Dr., MD A3–01, Research Triangle Park, NC 27709, T: 919–541–4253; F: 919–541–0295; e-mail: *shane@niehs.nih.gov*). Following the meeting, summary minutes will be available on the NTP web site and in hard copy upon request to the Executive Secretary. Plans are underway for making this meeting available for viewing on the Internet at (*http://www.niehs.nih.gov/external/video.htm*).

The NTP Board of Scientific Counselors Technical Reports Review Subcommittee meeting is open to the public. Attendance at this meeting is limited only by the space available. For planning purposes, individuals who plan to attend are asked to register with the NTP Executive Secretary (see contact information above). Registration will also be available on-site at the meeting. Persons needing special assistance, such as sign language interpretation or other reasonable accommodation in order to attend, are asked to notify the NTP Executive Secretary at least seven business days in advance of the meeting (see contact information above).

Draft Reports Available for Public Review and Comment

Approximately seven weeks prior to the meeting, the draft reports will be available for public review, free of charge, through ehpOnline (*http://ehp.niehs.nih.gov/*). Printed copies of the Draft NTP Technical Reports can be obtained, as available, from Central Data Management (NIEHS, P.O. Box 12233, MD EC–03, Research Triangle Park, NC 27709, T: 919–541–3419, F: 919–541–3687, e-mail: *CDM@niehs.nih.gov*).

Comments on any of the Draft NTP Technical Reports are welcome. Time will be provided at the meeting for oral public comment on the reports. Persons requesting time for an oral presentation on a particular report are asked to notify the Executive Secretary (contact information given above) by January 30, 2004, and to provide their contact information (name, affiliation, mailing address, phone, fax, e-mail), and supporting organization (if any). Persons registering to make comments are asked to provide a written copy of their statement to the Executive Secretary on or before January 30, 2004, to enable review by the Subcommittee and NTP staff prior to the meeting. These statements can supplement or expand an oral presentation. Each speaker will be allotted at least 7 minutes and, if time permits, up 10 minutes for presentation of oral comments. Each organization is allowed one time slot per report being reviewed. Registration for making public comments will also be available on-site. If registering on-site to speak and reading comments from printed text, the speaker is asked to provide 25 copies of the statement for distribution to the Subcommittee and NTP staff, and to supplement the record.

Written comments without an oral presentation at the meeting are also welcome. Comments should include contact information for the submitter (name, affiliation, mailing address, phone, fax, and e-mail) and supporting organization (if any). Written comments should be received by the Executive Secretary on or before January 30, 2004, to enable distribution to the Subcommittee and NTP staff for their review and consideration prior to the meeting.

Request for Additional Information

The NTP would welcome receiving toxicology and carcinogenesis information from completed, ongoing or planned studies as well as current production data, human exposure information, and use patterns for any of the chemicals listed in this announcement. Please send this information to Central Data Management at the address given above and it will be forwarded to the appropriate NTP staff.

NTP Technical and Toxicity Report Series

The NTP conducts toxicology and carcinogenesis studies of agents of public health concern. Any scientist, organization, or member of the public may nominate a chemical for NTP testing. Details about the nomination process are available on the NTP Web site (*http://ntp-server.niehs.nih.gov/*, select How to Nominate Substances). The results of short-term rodent toxicology studies are published in the NTP Toxicity Report series. Longer-term studies, generally, rodent carcinogenicity studies, are published in the NTP Technical Report series. The NTP has a new technical report series for studies conducted in genetically modified models. Study abstracts for all reports are available at the NTP Web site under NTP Study Information. PDF files of completed reports are available free-of-charge from ehpOnline under Publications and hard copies of published reports can be obtained through subscription to ehpOnline (*http://ehp.niehs.nih.gov/* contact information: T: 919–653–2595 or 866–541–3841, e-mail: *ehponline@ehp.niehs.nih.gov*).

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors ("the Board") is a technical

advisory body composed of scientists from the public and private sectors who provide primary scientific oversight and peer review to the NTP. Specifically, the Board advises the NTP on matters of scientific program content, both present and future, and conducts periodic review of the program for the purpose of determining and advising on the scientific merit of its activities and overall scientific quality.

The Technical Reports Review Subcommittee of the Board provides scientific peer review of the findings and conclusions of NTP Technical Reports. The Report on Carcinogens Subcommittee of the Board provides scientific peer review of nominations to the Report on Carcinogens, a Congressionally mandated listing of agents known or reasonably anticipated to be human carcinogens.

The Board's members are selected from recognized authorities knowledgeable in fields, such as toxicology, pharmacology, pathology, biochemistry, epidemiology, risk assessment, carcinogenesis, mutagenesis, molecular biology, behavioral toxicology, neurotoxicology, immunotoxicology, reproductive toxicology or teratology, and biostatistics. The NTP strives for equitable geographic distribution and for minority and female representation on the Board.

Dated: November 17, 2003.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

NATIONAL TOXICOLOGY PROGRAM (NTP) TECHNICAL REPORTS TENTATIVELY SCHEDULED FOR REVIEW BY THE NTP BOARD OF SCIENTIFIC COUNSELORS TECHNICAL REPORTS REVIEW SUBCOMMITTEE ON FEBRUARY 17–18, 2004 AT THE NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, RESEARCH TRIANGLE PARK, NC

Chemical/CAS No.	Report No.	Primary uses	Route and exposure levels	Review order
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)/1746–01–6.	TR 521	By-product of combustion and smelting.	Two-year study by inclusion in the diet at 3–100 ng/kg to female Sprague Dawley rats.	1
3,3',4,4',5-Pentachlorobiphenyl (PCB 126)/57465–28–8.	TR 520	Insulating fluid	Two-year study by inclusion in the diet at 10–100 ng/kg to female Sprague Dawley rats.	2
2,3,4,7,8–Pentachlorodibenzofuran (PeCDF)/57117–31–4.	TR 525	By-product of incineration and combustion.	Two-year study by inclusion in the diet at 3–100 ng/kg to female Sprague Dawley rats.	3
Mixture of PCB 126, TCDD, and PeCDF	TR 526	By-products of combustion, smelting and incineration.	Two-year study by inclusion in the diet at concentrations based on their toxic equivalency factors to female Sprague Dawley rats.	4
Malachite Green/569–64–2 and Leucomalachite Green/129–73–7.	TR 527	Dye and antifungal agent for fish.	Two-year study of Malachite Green by inclusion in the diet to female rats (100–600 ppm) and to male and female mice (100–450 ppm). Two-year study of Leucomalachite Green by inclusion in the diet to male and female rats (91 to 543 ppm) and to female mice (100–450 ppm).	5
Anthraquinone/84–65–1*	TR 494	Intermediate in dye synthesis	Two-year study by inclusion in the diet to male and female rats (469–3,750 ppm) and to male and female mice (833–7,500 ppm).	6
1. 1,2,3-Trichloropropane/96–18–4	TR 528	2. Paint and varnish Remover.	Exposure by aquarium water to Medaka and Guppy	7
2. 2,2,3–Bis(bromomethyl)-1,3-propanediol/3296–90–0.		3. Flame retardant.		
3. Nitromethane/75–52–5		3. Fuel additive, synthesis intermediate and solvent.		

*The draft NTP Technical Report on Anthraquinone was previously peer reviewed by the Subcommittee in May 1999. Subsequent to that peer review, the anthraquinone tested was found to contain a 0.1% contaminant. As a result, additional mutagenicity and metabolism studies were conducted and the findings from those studies are included in the revised draft report. The Subcommittee will evaluate the results from the follow-up studies, use that information to re-examine the carcinogenicity findings from the 2-year studies and make a recommendation on the carcinogenicity of anthraquinone.

[FR Doc. 03–30123 Filed 12–2–03; 8:45 am]
BILLING CODE 4140–01–P

DEPARTMENT OF THE INTERIOR

Fish and Wildlife Service

Notice of Availability of the Post-Delisting Monitoring Plan for the American Peregrine Falcon (*Falco peregrinus anatum*)

AGENCY: Fish and Wildlife Service, Interior.

ACTION: Notice of document availability.

SUMMARY: We, the U.S. Fish and Wildlife Service, announce the availability of the post-delisting monitoring plan for the American Peregrine Falcon (*Falco peregrinus anatum*). This plan is titled, "Monitoring Plan for the American Peregrine Falcon, A Species Recovered Under the Endangered Species Act" (Monitoring Plan). The American peregrine falcon was removed from the List of Endangered and Threatened Wildlife and Plants in August 1999 due to its recovery. The Endangered Species Act of 1973, as amended in 1988 (Act) (16 U.S.C. 1531 *et seq.*), requires that we implement a system, in cooperation with the States, to monitor effectively for at least 5 years, the status of all species that have recovered and no longer need the protection of the Act.

ADDRESSES: Copies of the Monitoring Plan are available by request from Michael Green, Migratory Birds and State Programs, U.S. Fish and Wildlife Service, 911 NE. 11th Ave, Portland, OR 97232. Requests may also be made via fax at 503–231–2019, or via telephone at 503–231–6164. This Monitoring Plan is also available on the World Wide Web at *http://migratorybirds.fws.gov* and *http://endangered.fws.gov/*.

FOR FURTHER INFORMATION CONTACT: Michael Green, Migratory Birds and State Programs, at the above address, at *michael_green@fws.gov*, or at 503–231–6164.

SUPPLEMENTARY INFORMATION:

Background

The American peregrine falcon occurs throughout much of North America, from the subarctic boreal forests of Alaska and Canada south to Mexico. American peregrine falcons nest from central Alaska, central Yukon Territory, and northern Alberta and Saskatchewan, east to the Maritime Provinces, and south (excluding coastal areas north of the Columbia River in Washington and British Columbia) throughout western Canada and the United States to Baja California, Sonora,

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program (NTP) Board of Scientific Counselors Technical Reports Review Subcommittee Meeting; Review of Draft NTP Technical Reports; Correction

The table included in the **Federal Register** notice (68 FR, No. 232 pp. 67696–67697) published December 3, 2003, had errors in the information provided in the column headed Route & Exposure Levels for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), 3,3',4,4',5-Pentachlorobiphenyl (PCB 126), 2,3,4,7,8-Pentachlorodibenzo-furan (PeCDF) and the Mixture of PCB 126, TCDD, and PeCDF. The corrected information is provided below.

Chemical/CAS No.	Report No.	Route & exposure levels
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)/1746–01–6.	TR 521	Two-year study; administered by gavage at 3–100 ng/kg to female Sprague-Dawley rats.
3,3',4,4',5-Pentachlorobiphenyl (PCB 126)/57465–28–8.	TR 520	Two-year study; administered by gavage at 30–1000 ng/kg to female Sprague-Dawley rats.
2,3,4,7,8-Pentachlorodibenzo-furan (PeCDF)/57117–31–4.	TR 525	Two-year study; administered by gavage at 6–200 ng/kg to female Sprague-Dawley rats.
Mixture of PCB 126, TCDD, and PeCDF	TR 526	Two-year study; administered by gavage at 10–100 ng TCDD "equivalents"/kg to female Sprague-Dawley.

Dated: December 19, 2003.

Samuel Wilson,

Deputy Director, National Toxicology Program.

[FR Doc. 04–100 Filed 1–2–04; 8:45 am]

BILLING CODE 4140–01–U

DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[NV–930–1430–ET; NVN–77821; 4–08807]

Notice of Proposed Withdrawal and Opportunity for Public Meeting; Nevada

AGENCY: Bureau of Land Management, Interior.

ACTION: Notice.

SUMMARY: The Bureau of Land Management has received a request from the United States Air Force to withdraw 1,979 acres of public land from surface entry and mining to protect support facilities for the safe and secure operation of national defense activities on the Nevada Test and Training Range. This notice segregates the land from surface entry and mining for up to 2 years while various studies and analyses are made to support a final decision on the withdrawal application.

DATES: Comments and requests for a meeting should be received on or before April 5, 2004.

ADDRESSES: Comments and meeting requests should be sent to the Nevada State Director, BLM, 1340 Financial Blvd., P.O. Box 12000, Reno, Nevada 89520–0006.

FOR FURTHER INFORMATION CONTACT: Dennis J. Samuelson, BLM Nevada State Office, 775–861–6532.

SUPPLEMENTARY INFORMATION: The United States Air Force has filed an application to withdraw the following described public land from settlement, sale, location, or entry under the general land laws, including the mining laws, but not the mineral leasing laws, subject to valid existing rights:

Mount Diablo Meridian

From the northwest corner of section 12, T. 5 N., R. 50 E., Proceed southeast 1,874.10 feet on a bearing of 155°48′00″ to starting point;
Thence southeast 5,551.20 feet on a bearing of 122°54′00″;
Thence northeast 15,530.30 feet on a bearing of 33°18′00″;
Thence northwest 5,551.20 feet on a bearing of 302°54′00″;
Thence southwest 15,530.30 feet on a bearing of 213°18′00″ to the starting point, excepting Tybo Road.

The area described contains 1,979 acres in Nye County.

The land would be withdrawn from settlement, sale, location, or entry under the general land laws, including the mining laws, but not the mineral leasing laws, to protect facilities that support the safe and secure operation of national defense activities on the Nevada Test and Training Range. Approximately 400 acres of the area are currently withdrawn by Public Land Order No. 6591, Parcel A (50 FR 10965–10966, FR Doc. 85–6479, March 19, 1985). Public Land Order No. 6591 will be allowed to expire as to Parcel A and will be replaced by this proposed withdrawal.

For a period of 90 days from the date of publication of this notice, all persons who wish to submit comments, suggestions, or objections in connection with the proposed withdrawal may present their views in writing to the Nevada State Director of the Bureau of Land Management.

Notice is hereby given that an opportunity for a public meeting is afforded in connection with the proposed withdrawal. All interested persons who desire a public meeting for the purpose of being heard on the proposed withdrawal must submit a written request to the Nevada State Director within 90 days from the date of publication of this notice. Upon determination by the authorized officer that a public meeting will be held, a notice of the time and place will be published in the **Federal Register** at least 30 days before the scheduled date of the meeting.

Comments, including the names and street addresses of those who submitted them, will be available for public review at the Tonopah Field Station, 1553 South Main Street, Tonopah, Nevada, during regular business hours 7:30 a.m. to 4:30 p.m., Monday through Friday, except holidays. Individual respondents may request anonymity. If you wish to hold your name or address from public review or from disclosure under the Freedom of Information Act, you must state this prominently at the beginning of your comments. Such requests will be honored to the extent allowed by law. All submissions from organizations or businesses, will be made available for public inspection in their entirety.

NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS

Technical Reports Review Subcommittee Meeting
Agenda

February 17 and 18, 2004
8:30 a.m. – 5:00 p.m.

National Institute of Environmental Health Sciences
111 T.W. Alexander Dr.
Research Triangle Park, NC

8:30 a.m.	Welcome	Dr. Christopher Portier, NIEHS and Dr. Mary Anna Thrall, Board Chair Colorado State University

Chemical/CAS #	Report Number	Primary Use, Route & Species
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD)/1746-01-6	TR 521	Byproduct of combustion and smelting Gavage, female rats
3,3',4,4',5-Pentachlorobiphenyl (PCB 126)/57465-28-8	TR 520	Insulating fluid for electronics Gavage, female rats
2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)/57117-31-4	TR 525	Byproduct of incineration and combustion Gavage, female rats
Dioxin mixture (PCB 126, TCDD, PeCDF)	TR 526	Insulator and combustion byproduct Gavage, female rats
Malachite Green/569-64-2 and Leucomalachite Green/129-73-7	TR 527	Dye; antifungal for fish Diet, Malachite Green - female rats, male and female mice Diet, Leucomalachite Green - male and female rats, female mice
Anthraquinone/84-65-1	TR 494	Intermediate in dye manufacture Diet, male and female rats and mice
1,2,3-Trichloropropane/ 96-18-4 2,2-Bis(bromomethyl)-1,3-propanediol/ 3296-90-0 Nitromethane/ 75-52-8	TR 528	Paint and varnish remover Flame retardant Fuel additive, synthesis intermediate and solvent Exposure by aquarium water to medaka and guppy

THE NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
Technical Reports Review Subcommittee Meeting
February 17-18, 2004

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Shuk-Mei Ho, Ph.D.
Professor of Surgery and Cell Biology
Department of Surgery, Division of Urology
University of Massachusetts Medical School
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***not in attendance

James E. Klaunig, Ph.D.
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Cheryl Lyn Walker, Ph.D. ***
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THE NATIONAL TOXICOLOGY PROGRAM
BOARD OF SCIENTIFIC COUNSELORS
Technical Reports Review Subcommittee Meeting
February 17-18, 2004

Ad Hoc Reviewers George Bailey, Ph.D. Distinguished Professor, Department of Environmental and Molecular Toxicology MFBS Center, 435 Weniger Hall Oregon State University Corvallis, OR 97331 Mac Law, DVM, PhD, Dipl. ACVP Associate Professor of Toxicologic Pathology, Aquatic Ecotoxicology North Carolina State University College of Veterinary Medicine Dept. of Population Health and Pathobiology 617 Hutton Street Raleigh, NC 27606	