Board of Scientific Counselors
National Toxicology Program

Summary Minutes
from
Peer Review of Draft Technical Reports of NTP
Toxicology and Carcinogenesis Studies of Electric and Magnetic Fields
by the Technical Reports Review Subcommittee

on
March 11, 1998

Research Triangle Park, N.C.

The meeting began at 9:00 a.m. on March 11 in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. Members of the Subcommittee are: Drs. Gary Carlson (Chairperson), John Bailer, Steven Belinsky, James Bus, Linda Chatman, John Cullen, Susan Fischer, Thomas Goldsworthy, Stephen Hecht, Michele Medinsky, and Jose Russo. Dr. Hecht was not present. Additionally, there were three *ad hoc* expert consultants present: Dr. Clinton Grubbs, University of Alabama/Birmingham; Dr. Martin Misakian, U.S. National Institute of Standards and Technology; and Dr. Maria Stuchly, University of Victoria, Canada. These minutes have been reviewed and approved by the Chairperson. They were written by Dr. Larry G. Hart, Executive Secretary.

When available, final NTP Technical Reports for the studies may be obtained through the Environmental Health Information Service (EHIS). Call 919-541-3841, Fax 919-541-0273, e-mail at ehis@nih.gov, or subscribe online at ehis@niehs.nih.gov.

The next NTP technical reports peer review meeting will be held October 30, 1998, in Research Triangle Park, North Carolina. For information, contact Dr. Hart, 919-541-3971.

SUMMARY MINUTES
NTP TECHNICAL REPORTS REVIEW SUBCOMMITTEE MEETING
March 11, 1998

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NTP Toxicology and Carcinogenesis Studies of Electric and Magnetic Fields

Introduction -- Dr. George Lucier, NIEHS, said the reports being reviewed today were part of an overall health assessment of electric and magnetic fields under the five year Electric and Magnetic Fields (EMF) Research and Public Information Dissemination (RAPID) Program authorized by Congress. There had been a workshop in March 1997 looking at the *in vitro* and mechanistic studies with EMF. A second workshop had been held in January 1998 evaluating EMF epidemiology studies, and a third workshop was scheduled for April which would evaluate*in vivo* animal studies, including the studies being reviewed here, and clinical studies. Dr. Lucier said that in June, a working group will meet and integrate all the different pieces of information into an overall report which will be the basis for a report by Dr. Olden to Congress later in the year. Dr. Olden's report will go through Secretary Shalala.

Orientation to the NTP Studies Process -- Dr. John Bucher, NIEHS, reported that the NTP is an interagency program, primarily centered at the NIEHS, with components from NCTR/FDA and NIOSH/CDC, and with the Director, Dr. Kenneth Olden, also being the Director, NIEHS. He described the NTP Executive Committee, which provides policy oversight, and noted that scientific oversight is provided by the NTP Board of Scientific Counselors, of which this Subcommittee is a component. The overall goals are (1) to provide toxicological evaluation of substances of public health concern, (2) to develop and validate improved toxicology methods, (3) to develop approaches and generate data for strengthening the science base for performing risk assessments, and (4) to communicate our findings to all of our stakeholders. The NTP studies primarily chemicals, classes of chemicals or mixtures of chemicals, but also physical agents such as EMF. The Program has a reputation for generating data on carcinogenicity of agents, but also has extensive studies in general toxicology, genetic toxicology, reproduction and development, neurotoxicology, immunotoxicology, and pulmonary/respiratory function. Where possible, information is obtained from mechanistic studies that will help interpret standard studies. Dr. Bucher described the chemical nomination and selection process. Once a chemical is selected, a project leader is assigned; in this particular instance, Dr. Gary Boorman, NIEHS, is the project leader for EMF and EMF-related studies. The information collected by the project design team is integrated into a protocol, which goes through internal review, and then usually the studies are conducted in contract laboratories according to the NTP statement of work for toxicology and carcinogenesis studies, and under Good Laboratory Practices (GLP) of the FDA and EPA. Dr. Bucher described the designs of the carcinogenesis studies, which are flexible but include a standard core study that includes adequate numbers of animals for statistical power and adequate duration for expression of induced cancers, usually two years. Principal endpoints evaluated are the pathology endpoints. The pathology materials undergo a three step evaluation. The first step is that the study pathologist reads the entire study. Second, a quality assurance pathologist reviews all of the tumors diagnosed by the original study pathologist and reviews all tissues with possible treatment related effects. The third step involves convening of a pathology working group, usually eight to ten pathologists, to review representative lesions and all descrepancies in diagnoses between the quality assurance pathologist and original study

pathologist. The last stages include public peer review of draft technical reports by the Subcommittee, and finally publication of findings as final technical reports and journal articles.

Draft Technical Report Reviews

Two Year Toxicology and Carcinogenesis Studies on EMF in F344/N Rats and B6C3F$_1$ Mice of Both Sexes. Dr. Boorman discussed the rationale for initiating these studies. In 1979, a report in the *American Journal of Epidemiology* (Wertheimer and Leeper) noted that childhood leukemia was increased in homes that had a high wire code configuration. Another study published in the same journal (Savitz) in 1988 was confirmatory. Based on these findings, the Department of Energy (DOE) and the Electric Power Research Institute (EPRI) nominated magnetic fields to the NTP for study in 1988. In 1990, the National Association of Regulatory Utility Commissioners also requested a study. The decision was made to conduct standard toxicology studies and long-term carcinogenesis studies using the rodent model. Since the NTP had not much experience in this area, Dr. Boorman reported that draft protocols were sent to many scientists within and outside of the Government soliciting comments and advice. There was a consensus that the study should focus on 60 Hertz (Hz) sine waves as this represented the predominant human exposure. The low field intensity chosen was 20 milligauss (mG) which is about 10-times what is considered a high residential exposure, while the high intensity chosen was 10 gauss (G), perhaps the maximum that could be achieved for a large animal study, and the intermediate intensity was 2 G. Dr. Boorman described in some detail the layout and characteristics of the exposure facility and the scheme for the rotation of animals. Once the facility was set up, a number of short-term animal studies were conducted including an eight week toxicity study, a developmental toxicity study, and a reproductive toxicity (six month continuous breeding) study. Results have been published or submitted for publication.

Dr. Boorman turned to a discussion of the two toxicology and carcinogenesis studies. He noted that from the more than 40 epidemiology studies, the potential cancer sites that have been identified in humans are leukemia, lymphoma, breast cancer and brain cancer. The study pathologist looked at 43 tissues but the reviewing pathologists looked at all potential sites for leukemia, lymphoma, breast cancer, andbrain cancer. In male rats there was a decreased incidence of mononuclear cell leukemia in the 10 G intermittent group. In neither rats nor mice were there any unequivocal positive findings. Dr. Boorman pointed out that the only exposure group where there was an increased incidence of neoplasms was male rats where thyroid C-cell adenomas and carcinomas were marginally increased over controls, with statistical significance in low (0.02G) and mid exposure (2.0G) animals. Conversely, there was a reduction (not significant) in thyroid C-cell hyperplasias. Dr. Boorman concluded his remarks by presenting arguments for and against an association of these tumors with magnetic field exposure. Arguments for an EMF effect include (1) both adenomas and carcinomas were increased, (2) two exposure groups were affected, (3) decreased hyperplasias and increased neoplasms could argue for a promotional effect, and (4) there appeared to be no confounders. Arguments against an EMF effect included (1) no increases at the higher field intensities, (2) no increases in female rats, (3) decreased

hyperplasias, (4) neoplasms are within the historical control rates by other routes of administration, (5) rates typically are quite variable, (6) not an expected site based on epidemiology studies, and (7) no effect in mice other than significantly decreased incidences of malignant lymphomas in female mice (10 G exposure group) and pulmonary neoplasms in male and female mice in the 2 G exposure groups. Thus, the conclusions for the two-year studies in mice and rats were that:

> Under the conditions of these 2-year whole-body exposure studies, there was *equivocal evidence of carcinogenic activity* of 60-Hz magnetic fields in male F344/N rats based on slightly increased incidences of thyroid gland C-cell neoplasms. There was *no evidence of carcinogenic activity* in female F344/N rats or male or female $B6C3F_1$ mice exposed to 0.02, 2, or 10 G, or 10 G intermittent 60-Hz magnetic fields.
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> In exposed rats and mice there were no increased incidences of neoplasms at sites for which epidemiology studies have suggested association with magnetic fields (brain, mammary gland, leukemia).

Dr. Cullen, a principal reviewer, agreed with the conclusions. He thought the use of two or multiple sections of the thyroid along with the use of a new diet might impact on comparisons with the historical control database. Dr. Boorman said that because some second cuts had to be made for some rats, to eliminate bias second cuts were done on all the thyroids. He agreed that double sectioning along with use of the new diet lessened the usefulness of the historical controls for comparisons. Dr. Cullen wondered at what things were looked at in the pineal gland since this not an organ routinely examined. Dr. Boorman said that we became more familiar with pineal histology. Dr. Cullen observed that some discussion of the effect of the age differences between weaned animals of 6 to 8 weeks of age and human neonates in their sensitivity to EMF effects might be considered. Dr. Boorman said that was a good point but Dr. Rosemond Mandeville had looked at the effects of exposures beginning on the 20th day of gestation, through parturition, and weaning in female rats.

Dr. Bus, the second principal reviewer, agreed in principle with the conclusions. He suggested that since the unexpected thyroid tumor finding seems unlikely to be attributable to magnetic field exposure, the NTP should consider emphasizing this point in the Conclusions with wording changes or addition of a sentence. Dr. Boorman said he would look at that and try to put more balance into the discussion. Dr. Bus commented that there were sentences in the discussion that imply that the findings of the current study are not consistent with associations of magnetic field exposures and human childhood and adult leukemias. Though correct, since the study design did not include pre- or early post-natal exposures, he said the findings of this study may not be particularly relevant to implications of human childhood leukemias.

Dr. Bailer, the third principal reviewer, agreed in principle with the conclusions. He noted other dose-related increases in male rats, in particular the skin trichoepitheliomas and

basal cell adenomas, and as well, skin squamous cell papilloma and keratocanthoma, and asked whether these results might not support **some evidence**. Dr. R. Hailey, NIEHS, explained that the relevant analysis is a combined analysis of these skin neoplasms as they are all thought to be derived from basal epithelium. Dr. Haseman said that if one looks at the final tumor combination, which is most relevant, there are more tumors overall in the control group than in the exposed groups. Dr. Bailer said that these reasons need to be shared in the report.

Three *ad noc* expert consultants were present to assist with the reviews. They were Dr. Clinton Grubbs, University of Alabama/Birmingham, Dr. Martin Misakian, US National Inatitute of Standards and Technology (NIST), and Dr. Maria Stuchly, University of Victoria. Dr. Stuchly said the report comprehensively describes the study design, results and data analysis and the essential findings were properly addressed. She said that from her engineering viewpoint, the only limitation was poor quantification of the exposure conditions. Particularly, the maps of field uniformity within the space occupied by the animals were not provided, and the contract facility has the capability to compute uniformity of exposure fields. Dr. Boorman agreed to add an appendix that detailed the exposure conditions. Dr. Stuchly stated that there is also a question of calculation of the dose, noting that such computations have been done for the human body, and a good model of the body for the rat but not the mouse so perhaps the rat data could be used for the mouse. Dr. Misakian wanted to respond to Dr. Stuchly's concerns about the field conditions. He said that during site visits by NIST, the uniformity was characterized by measuring on each shelf where animals were located and on a perimeter line that enclosed the area. About 18 measurements were made on the perimeter and compared with the field value at the center of that shelf. All of the field values that were measured were within 10% of the targeted field levels reported. Dr. Misakian discussed the differences between circularly polarized and linearly polarized magnetic fields, and both he and Dr. Stuchly agreed that people are primarily exposed to linearly polarized magnetic fields.

Dr. Cullen moved that the Technical Report on whole-body exposures with 60-Hz magnetic fields be accepted with the conclusions as written for male rats, **equivocal evidence of carcinogenic activity**, and for female rats and male and female mice, **no evidence of carcinogenic activity**. Dr. Bus seconded the motion. There was some discussion as to whether "slightly increased incidences of thyroid gland C-cell neoplasms." should be modified by deleting "slightly". Dr. Bucher suggested "occurrence of" instead of "slightly increased incidences" as less directly associating the neoplasms with the exposures. In response to a query by Dr. Cullen, Dr. Haseman said the P value for low and mid dosed groups under "Adenoma or Carcinoma" was less than 0.01. Dr. Bus said there needs to be a word or word that qualifies why the call is **equivocal**. Dr. Medinsky noted that the definition of "equivocal" in the report uses the word "marginal" so marginal defines equivocal. Dr. Bailer moved to amend the motion by deleting "slightly". Dr. Medinsky seconded the amendment, which was accepted by seven yes votes to one no vote (Bus) with one abstention (Goldsworthy). Dr. Bus stated that there still needed to be wording suggesting a non-exposure related increase in C-cell neoplasms. Dr. Haseman suggested identifying the specific dose groups where the increase was seen. Dr. Bailer moved to

further modify his original amendment to read "based on increased incidences of thyroid gland C-cell neoplasms in the 0.02 G and 2.0 G exposure groups." Dr. Russo seconded the amended motion, which was accepted by eight yes votes with one abstention (Goldsworthy).

Three DMBA Initiation/Magnetic Field Promotion Studies in Female Sprague Dawley Rats. Dr. Boorman said that the initiation/promotion studies were supported by the EMF RAPID Program, which as Dr. Lucier had mentioned, was mandated by the Congress and coordinated through DOE. He said that when EMF and cancer issues were looked at, the three areas of concern were leukemia, brain cancer, and breast cancer. EPRI is addressing leukemia with a large mouse study. Brain cancer is the focus for a large mouse study through an extramural grant with U.C.L.A. With regard to breast cancer, Dr. Boorman cited epidemiology studies highlighting male breast cancer in electricians, and small associations of occupation in females with increased incidence of breast cancer. He discussed studies that report EMF can block melatonin inhibition of cell growth and lower nocturnal melatonin levels in rodents. Dr. Boorman summarized the findings from a series of studies by Loscher on magnetic field promotion of dimethybenzanthracene (DMBA) initiation of breast cancer in female Sprague Dawley rats. In these studies, DMBA initiation involved a single dose of 5 mg at 50 days of age followed by 5 mg for each of three weeks. Then the animals were exposed to 50 Hz (European frequency) sine wave magnetic fields for 13 weeks with palpation for tumors weekly. Field intensities ranged from 3 mG up to 300 G. Statistically significant increases in mammary tumors were reported only in groups exposed to 500 mG and 1 G. Further, Loscher published a histological diagnosis comparing control animals with exposed which indicated no increased incidences of hyperplasia, atypia, adenomas, fibroadenomas, or carcinoma *in situ*.. There was a statistically significant increase in adenocarcinomas. Thus, after consultations with outside experts including our EMF advisory committee, Dr. Boorman said the first series of NTP studies would be to replicate the Loscher experiments.

The first 13-week (13-I) study went to great lengths to replicate all of the experimental conditions including lighting used in the Loscher study. Female Sprague Dawley rats were used with 100 animals/group. The groups included vehicle controls, DMBA controls, DMBA + 1 G/50 Hz, DMBA + 5 G/50 Hz, and DMBA + 1 G/60 Hz. Evaluations included weekly palpations for tumors and melatonin measurements at 4, 8, and 12 weeks. Necropsy included both gross and microscopic evaluation of mammary lesions, and any lesions in lung, liver and kidney. Measurements of tumor numbers and size were done as precisely as possible. There was no difference in times to tumors between DMBA controls and EMF exposed groups with first tumors seen at seven weeks and rapid increases in numbers after 13 weeks. Some of Loscher's work shows earlier occurrences in EMF exposed animals. Dr. Boorman said there were no differences between DMBA controls and exposed groups in incidences of carcinomas, in total numbers of carcinomas, and in tumor area/rat. In the DMBA + 1 G/50 Hz, there were significantly fewer numbers of carcinomas.

The second 13-week (13-II) study was similar to 13-I except that DMBA doses were 2 mg, only mammary lesions were evaluated, and there was no vehicle control group as there

had been no mammary tumors found in vehicle controls from 13-I. Like 13-I, although incidences and tumor numbers were lower with the 2 mg doses of DMBA, there were no differences between DMBA control and EMF exposed groups in incidences, numbers of carcinomas, and tumor area.

The 26-week study was a more traditional study which allowed more time for promotional effects, especially weak ones, to occur. There was a single 10 mg dose of DMBA. The times to tumors were similar to 13-I, and by 26 weeks there was about 90 % incidences in DMBA controls and EMF-exposed groups. With regard to numbers of carcinomas, the highest number was in the DMBA control, while there were statistically significant fewer numbers in the groups exposed to 1G/50 Hz and 1 G/60 Hz. Mean carcinoma area per rat was fairly similar across groups. Thus, the conclusions for the initiation/promotion studies in female rats were that:

> In an initiation/promotion study in which female Sprague Dawley rats were initiated by four weekly doses of 5 mg DMBA per rat beginning at 50 days of age and exposed to 50-Hz magnetic fields at 1 or 5 G field intensities or to 1 G 60-Hz magnetic fields for 13 weeks, there was **no evidence** that magnetic fields promoted the development of mammary gland neoplasms. The prevalence and multiplicity of mammary gland carcinomas in all DMBA groups limited the ability of this assay to detect a promoting effect of magnetic fields.
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> In an initiation/promotion study in which female Sprague Dawley rats were initiated by four weekly doses of 2 mg DMBA per rat beginning at 50 days of age and exposed to 50-Hz magnetic fields at 1 or 5 G field intensities for 13 weeks, there was **no evidence** that magnetic fields promoted the development of mammary gland neoplasms.
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> In an initiation/promotion study in which female Sprague Dawley rats were initiated by a single 10 mg DMBA dose at 50 days of age and then exposed to 50-Hz magnetic fields at 1 or 5 G field intensities or to 1 G 60-Hz magnetic fields for 26 weeks, there was **no evidence** that magnetic fields promoted the development of mammary gland neoplasms.

Dr. Russo, a principal reviewer, agreed with the conclusions. He noted that in figure 7 where the mean number of tumors per tumor bearing animal is plotted against time, it takes four more weeks for animals exposed to magnetic fields to reach the same number of tumors as DMBA control animals. In figure 8, mean tumor size is delayed in animals exposed to magnetic fields. Dr. Russo said this suggests that EMF exposure retards rather than accelerates growth of these lesions, and this should be discussed more thoroughly in the report.

Dr. Chatman, the second principal reviewer, agreed with the conclusions. She commented that it was not clear whether or not distance from the source to the animal was included in the definition of exposure. If it was then this should be stated and attention given to

making it consistent. Dr. Boorman said the exposure would be better defined. He said the animals were in a field that was uniform, and there were coils around the field so as the animals moved around in cages, they stayed within a field. Dr. Chatman said that her veterinary background made her wonder whether there had been any observations made as to cancer in pets in homes where cancer was associated with EMF. Dr. Boorman said he was not aware of any data on companion animals.

Dr. Fischer, the third principal reviewer, agreed with the conclusions. She observed that the Loscher experiments all used 24-hour exposure times while the current NTP experiments all used 18 1/2- hour exposure times, and said there is a need to assess the importance of this difference in the outcomes. Dr. Boorman said our daily exposure time allowed adequate time for the technicians to conduct animal care without being exposed themselves. He noted that the exposure hours in the 26-week study would have exceeded or been equivalent to Loscher's 13-week, 24-hour per day exposure regimen. Dr. Fischer thought that the differences in tumor size should be given more attention especially as noted by Dr. Russo, there was a suggestion of a protective effect of magnetic fields with regard to tumor growth rates.

Comments were taken from the *ad hoc* expert consultants. Dr. Stuchly said she had been concerned by the high tumor incidences in the first 13-week study, higher than in the Loscher study, but thought that the second 13-week and 26-week experiments better allowed for detection of possible promotional effects. She commented that the review of the epidemiological studies was too brief and needed to be expanded to include studies that gave negative results. Dr. Boorman said he would flesh out the listing of epidemiology studies to give more completeness. Dr. Stuchly said that the statement that the effects of the Loscher studies were "marginal" is at odds with Loscher's interpretation and may need to be reconciled. Dr. Boorman agreed and said he would remove the editorial comment about the "marginal" effects seen in the Loscher study and let the data speak for themselves. Dr. Grubbs said this was well designed study conducted in excellent facilities by a highly qualified and competent staff, and the data were fairly conclusive. He noted that a certain number of rats in each group did not survive until the end of the study and that it would be helpful to know the reasons, and said that a survival curve graph would be helpful. Dr. Boorman said there was only one death in the second 13-week study. In the other studies, about 8-12 animals died per group with about half being moribund and half occurred as natural deaths due to ulcerated tumors. Dr. Grubbs argued for presenting the data on tumor size and tumor numbers differently; in other words, he would divide the tumor size of all the rats in a group by the number of rats in the group, usually 100, to obtain the mean whether the rats had a tumor or not. This same approach could be used in estimating mean tumor number.

Dr. Cullen commented that one of the definitions of promotion is generation of an earlier onset of tumors, which is not the case here, but also a higher number or increased yield of tumors. He wondered how an increased yield could be detected when there was such a high incidence. Dr. Boorman responded that they were counted and confirmed histologically. Drs. Russo and Fischer also emphasized that in a typical initiation/promotion

study where incidence of tumor bearing animals is quite high, multiplicity or numbers of tumors become important in discerning whether or not there is an effect. Dr. Boorman agreed noting that having the tumor multiplicity data along with time to tumor and tumor size information enabled us to confidently conclude that magnetic fields did not have tumor promoting effects.

Dr. Russo moved that the Technical Report on three DMBA initiation/magnetic field promotion studies in female Sprague Dawley rats be accepted with revisions as discussed and with the conclusions that there was **no evidence** that magnetic fields promoted the development of mammary gland neoplasms. Dr. Chatman seconded the motion, which was accepted by eight yes votes with one abstention (Goldsworthy).