Attachment V – Biological Search and Results

Over the past several decades, there has been concern about a possible relationship between exposure to electromagnetic fields and links to cancer development and health effects. Concerns have been expressed about exposure to electrical energy /electromagnetic radiation from sources such as power distribution and transmission lines (extremely low frequency [ELF] 50Hz magnetic fields) as well as from occupational sources (navigation and surveillance equipment), household wiring, microwaves, and cell phones. The potential for genotoxicity and mutagenicity has been studied and reported extensively in the literature.

References obtained from both the original search (3) as well as new literature searches are outlined below. These were reviewed to assess the incidence or risk of possible biological effects from electrical stimulation. Searches were conducted using PubMed to obtain additional information regarding risks associated with electrical stimulation at the biologic level, including information on carcinogenicity, mutagenicity, cell toxicity, and teratological effects. Results were restricted to English language articles only. Combinations of the following keywords were used:

- Pulsed electromagnetic fields
- Capacitively coupled
- Capacitively coupled electric field
- Electromagnetics
- Electromagnetic fields
- Mutagenicity
- Carcinogenicity
- Biological effects
- Teratology
- DNA
- 60 KHz

The number of citations which resulted from various keyword combinations is listed in the table below. Initially, titles were reviewed for pertinence. In come cases, related articles to titles of interest were also reviewed as indicated. Subsequent to the title review, abstracts of selected articles were reviewed and specific articles were obtained for in-depth analysis.

Table 1. Literature Searches for Biological Effects of Electrical Stimulation

Keyword Combinations	Number of Citations	Review of Related Articles*
Pulsed electromagnetic fields OR capacitively coupled OR electromagnetics OR electromagnetic fields AND mutagenicity OR genotoxicity OR DNA	780,770	--
Pulsed electromagnetic fields OR capacitively coupled OR	5	814 of 2,570

electromagnetics OR electromagnetic fields AND mutagenicity AND DNA		
Capacitively coupled electric field AND biological effects	4	--
Pulsed electromagnetic fields OR capacitively coupled OR capacitive coupling OR 60KHz AND biological effects	98	--
Pulsed electromagnetic fields OR 60 KHz AND mutagenicity	4	--
Pulsed electromagnetic fields OR 60 KHz OR mutagenicity	3	--
Pulsed electromagnetic fields AND teratology	4	--
Carcinogenicity AND electromagnetic fields	25	--

*Next to each citation is the category of "Related Articles". This category was explored for additional citations that may have been pertinent.

Given the extensive number of articles obtained from the first search, additional keyword combinations were employed to narrow the focus. There was overlap between the various searches. Titles were reviewed and 23 abstracts were chosen for further review. Twenty complete articles were obtained (3 originated from the original reclassification petition search of 165 references). A discussion and outline of 16 of these articles (13 from the new search and 3 from the original search) is presented summarizing the present understanding of the biological effects of electrical energy/electromagnetic fields. Two of these are in-depth review articles of the subject that were identified during this new search and these provide a comprehensive summary of the literature in this area. A third review article of the subject focuses on the subject and its relevance to the frequencies used in bone stimulation therapy (Bassett, 1989). This article originated in the original reclassification petition search.

Most of the citations were associated with exposure to electrical energy /electromagnetic radiation from sources such as power distribution and transmission lines (extremely low frequency [ELF] 50Hz magnetic fields). In the literature, concerns are also expressed about exposures from occupational sources (navigation and surveillance equipment), household wiring and appliances, and communication equipment (cell phones) and the possible relationships to cancer. There were few articles focused upon frequencies attributed to sources used for bone growth stimulation. From the overall information, clear evidence does not exist establishing a link between exposure to these sources and cancer in humans.

Biological Effects of Electrical Stimulation – RS Medical has conducted a literature search to investigate whether any biological effects of electrical stimulation, including carcinogenicity, mutagenicity, cell toxicity, and teratological effects, have been consistently described in the literature and how to best characterize these theoretical risks as part of the risk analysis process. A summary of the literature search methodology and its findings are provided above. Attachment X includes a bibliography of the articles cited in this response.

Over the past several decades, there has been concern regarding the possible relationship between exposure to electromagnetic fields and adverse biological effects, such as cancer development. Concern has been expressed about exposure to electrical energy /electromagnetic radiation from sources such as power distribution and transmission lines (extremely low frequency [ELF] 50Hz magnetic fields), as well as from occupational sources (navigation and surveillance equipment), household wiring, microwaves, and cell phones. The potential for genotoxicity and mutagenicity has been studied and reported extensively in the literature.

Carcinogenicity, Mutagenicity, and Genotoxicity

References obtained from both the original literature search described in the petition, as well as new literature searches described above are summarized here. Most of the citations regarding potential carcinogenicity were associated with exposure to electrical energy /electromagnetic radiation from sources such as power distribution and transmission lines (extremely low frequency [ELF] 50Hz magnetic fields). Concerns are also expressed about the relationship of occupational sources of exposure to cancer development. These sources include: navigation and surveillance equipment; household wiring and appliances; and, communication equipment (cell phones). Combined effects of frequencies on the initiation and promotion of cancer caused by known carcinogens have also been studied. From the overall information, solid evidence does not exist establishing a clear link between exposure to these sources and cancer in humans.

The International for Research on Cancer (IARC), which is part of the World Health Organization, has reviewed available evidence and classified relative exposures of humans to static and ELF electric and magnetic fields and their association to cancer risk (IARC Monogr Eval Carcinog Risks Hum. 2002;80:1-395). A brief summary of this work is also available (J.Radiol Prot. 2001;21:313-314). A clear link between exposure and increased cancer incidence has not been demonstrated. Some epidemiological studies exist in which a connection is claimed, however, selection bias cannot be ruled out. Evidence from long-term animal bioassays has not shown positive results either and has been determined to be inadequate. Based upon the available information, several conclusions were drawn. The IARC concluded that: the association between childhood leukemia and high residential magnetic field strengths is limited evidence for excess cancer risk in humans; there is inadequate evidence that residential and occupational exposures are related to increased risks of cancers; and, the overall evidence from long-term animal bioassays of the effects of ELF magnetic fields in animals is inadequate. Studies on static magnetic fields and static or ELF electric fields were not available for review. Overall, ELF magnetic fields were designated as "possibly carcinogenic to humans" (Group 2B) and static magnetic fields and static and ELF electric fields could not be classified as to the carcinogenicity (Group 3). Other experts have also concluded that possible associations between electric or magnetic fields and childhood leukemia remain unexplained (Brain et al., 2003). A

mechanism for cancer initiation by electromagnetic fields has not been developed. Furthermore, negative results are mainly produced in laboratory animals which does not lend support to a connection. Key exposure parameters remain to be determined and continued evaluation in animal models is necessary.

The body of evidence in the literature regarding tests of magnetic fields in animal models (in vivo) of carcinogenesis (2-year, lifetime, and multigenerational exposure) was also reviewed (McCann et al., 2000). Individual reports were assessed according to reproducibility and data quality. Negative results are consistent and have been reproduced in chronic bioassays and in promotion and copromotion assays. Independent reproducibility has not been observed for reports of positive results. It was concluded in this comprehensive review that long-term, continuous exposure to 50 or 60 Hz magnetic fields (0.002 – 5mT) is unlikely to be carcinogenic in rats or mice. Weak promoting effects of magnetic fields could not be ruled out with the evidence reviewed, however, based on the available reports. These views are also expressed in an earlier review of the available genotoxicity and carcinogenicity literature (Juutilainen and Lang, 1997).

Most of the literature reports evaluate the effects of ELF magnetic fields because of the extent of exposure of humans to power lines and an early study which discussed a relationship between such exposure and childhood leukemia. Genotoxic and mutagenic potential have been evaluated in bacterial cells, in vitro chromosome assays, and in vivo chromosome or DNA repair assays. The table provided later in this response shows some examples of reported work, but is not intended to be extensive or comprehensive. Several comprehensive reviews of the literature in this area already exist and are included below, providing conclusions currently available in this area of investigation. An independent, extensive assessment of this literature base would not appear to be necessary in the assessment of the theoretical risks pertinent to this petition. The citations presented in the table below illustrate the variety of exposure conditions tested and exposure of both bacterial and mammalian cells. Most frequently, the Ames test is utilized. Negative results are consistently produced with the variety of exposures. If an increase in the temperature (thermal effect) is not caused by the exposure, positive (genotoxic/mutagenic) results are not observed.

Work in the area of genotoxicity has also been reviewed comprehensively twice (McCann et al., 1998). Electric and magnetic field exposures were grouped into six categories: ELF fields; ELF magnetic fields; combined ELF electric and magnetic fields; static electric fields; static magnetic fields; and, co-exposures to electric and magnetic fields and ionizing radiation, UV light, or chemical mutagens. Studies of ELF magnetic fields are prevalent. Their first review of 55 studies was published in 1993. Subsequently in 1998, the authors updated the review with 29 additional articles for a total of 84 articles. The published studies were evaluated on independent reproducibility, consistency with the scientific knowledge base, and completeness. Between these two comprehensive reviews, 34 articles reported positive effects, but these studies could not or have not been duplicated. There is a relatively larger number of reports in which negative results are presented and independently confirmed. Overall, the authors conclude that preponderance of evidence at this point suggests that these exposures are not genotoxic to bacterial or mammalian cells or in the in vitro or in vivo (DNA strand breaks, chromosomal

damage) test systems. The reports in which positive effects were observed require independent confirmation.

Similar conclusions were drawn from another comprehensive review (Brusick et al., 1998). Data from studies in which the integrity of nucleic acids were tested following exposure to a frequency range of 800 to 3,000 MHz were reviewed using a weight of evidence approach. Patterns or trends were used to develop conclusions with this analysis. Over 100 studies were reviewed. Chronic exposure to radiofrequency radiation and the direct and indirect effects on DNA were examined. The available database included frequencies in the range of wireless communication devices (800 MHz to 2,000 MHz), microwave ovens (2,450 MHz), and RFRs ranging from 300 Hz to 30,000MHz. Details for the studies were tabulated. Test systems included in vitro bacterial and in vivo in drosophila and mammalian cells. Mutation frequency, chromosomal aberrations, micronucleus formation, sister chromatid exchange, DNA damage/repair, sperm abnormalities and cell transformation were studied. Exposure conditions across the studies present the most confounding variable. Exposure conditions were not always uniform and cannot always be monitored accurately making it difficult to compare doses. An increase in the temperature caused by exposure to the fields influences the outcome, causing positive results. Most studies do not report genotoxic effects. Gene mutation or recombination does not appear to be affected. It is concluded that RFRs in the range of 30 MHz to 30,000 MHz do not pose a hazard. These authors conclude at this time that the data do not indicate a genotoxic risk from exposure. Limited animal cancer studies are available (2,450 MHz, 915 MHz) and have not shown an increase in carcinogenicity, although there is work showing tumor enhancement in a mouse model. Overall, under normal exposure conditions, it is concluded that there is not a risk, if thermal effects do not occur.

Biological effects of exposure to high-frequency electromagnetic radiation have been investigated in a variety of species. Potential effects at the genetic level are studied do to the available standardized assays and the possibility that induced mutations may contribute to eventual carcinogenicity. As mentioned above, there has been discussion regarding whether some positive effects observed were due, in fact, to a rise in the temperature elicited by the radiation. The evidence has been reviewed extensively as discussed above. Recent reports also confirm these findings. Although standardized test systems were employed, exposures varied among the experiments. Seven studies are outlined in the table on the next page. Genetic damage in *Salmonella typhinurium* and *Drosophila melanogaster* was examined following exposure to radiofrequency electromagnetic fields (Hamnerius et al., 1985). Four exposure conditions were studied and no elevation in reversions or somatic mutations was observed. An increase in cell growth was noted. Similar effects were reported by others with regard to mutation frequency (Chahal et al., 1993; Morandi et al., 1996; Jacobson-Kram et al., 1997; Nakasona et al., 2000; and Schreiber et al., 2001). No increase in mutagenic activity was observed. DNA damage in human cells was assessed more recently and no effects were reported (Testa et al., 2004). These articles represent an example of the available literature, illustrating the type of reports available in the literature, the variety of exposures, and reproducibility of results from the systems evaluated. Some of these reports were also covered in the comprehensive review articles, while others are more recent.

Table 2. Example Articles on the Genotoxic and Mutagenic Potential of Electrical and Magnetic Fields

Reference	Species/Organism	Exposure/Dosimetry	Time	Effects
Hamnerius et al., 1985	Ames Test *Salmonella typhinurium* *Drosophila melanogaster*	27.12-MHz CW electric field 27.12-MHz CW magnetic field Microwave irradiation 2.45 GHz modulated EMR (far field) (power lines and microwave ovens) 3.10-GHz pulsed EMR(far field) pulse repetition of 500Hz and duration of 1μs	*Salmonella* 2.5 to 6 hours *Drosophila* 6 hours	No elevated reversions (no increase in mutations) in *Salmonella* Increased growth No increase in somatic mutations in eukaryotic *Drosophila*
Bassett, 1989 *#12	Swiss-Webster Mouse sarcoma model Case reports of pathological fractures in bone cancer patients	PEMFs PEMFs	Chronic/1 year NR	Length of survival, number & type of tumors is the same. Bony union, no increase in malignant process up to10 years (2 cases
Chahal et al., 1993	*Escherichia coli*	1Hz 3kV/m 1kV/m	1 hour 16 hours	No increase in mutation frequency No increase in mutagenic effects of UV radiation or mitomycin C
Morandi et al., 1996	Ames Test *(Salmonella typhinurium)*	Combined field frequencies of 60, 600, 6000 Hz electric field, magnetic field and combined	48 hours	Rate mutation not affected
Jacobson-Kram et al., 1997	Ames Test *(Salmonella typhinurium, Escherichia coli)* In vitro (CHO) chromosomal aberration assay BALB/3T3 cell transformation Unscheduled DNA synthesis rat hepatocytes	Orthofix (AME) PEMF implantable stimulator 99 pulses at 1.5 pulse bursts per sec. Low dose: clinical dose positive amplitude 3mV/cm, 1mV/cm negative amplitude High dose: 10 times low dose	24 hours	No toxicity or mutagenic activity No increase in mitotic index aberration frequency No affect on cloning efficiency, transforming frequency No measurable toxicity nor increase in unscheduled DNA synthesis
Nakasona et al., 2000	Ames Test *(Salmonella typhinurium, Escherichia coli)*	50 Hz, 14 mT circularly polarized magnetic field	48 hours	No mutagenic or co-mutagenic potential.

Table 2. Example Articles on the Genotoxic and Mutagenic Potential of Electrical and Magnetic Fields (Continued)

Reference	Species/Organism	Exposure/Dosimetry	Time	Effects
Schreiber et al., 2001	Ames Test *(Salmonella typhinurium)*	1.5 Tesla Clinical MR scanner (with ELFMGFs; RF magnetic field, with / without chemical mutagens) 7.2 T (with/without chemical mutagen)	1 hour 24 hours	No mutagenic effect or co-mutagenic effect
Testa et al., 2004	DNA damage in Human blood cells Comet assay Sister Chromatid exchange Chromosomal aberrations Micronucleus test	ELFMF 50 Hz 1mT magnetic fields (with / without x-rays 1Gy)	48 hours	No DNA damage No effect on cell proliferation No synergistic or antagonistic effect with ionizing (X-rays) radiation

*Included in the original reclassification search bibliography of 165 references, #Review Article

Having presented evidence from the literature associated with common environmental electromagnetic exposures (power lines, communications devices, and R.F.s, and microwaves), it should be noted that the therapeutic PEMF frequencies, which are the subject of this reclassification petition, differ substantially from these. PEMFs are intended to simulate a range of frequencies which occur naturally in the body. Thus, the bulk of the available literature does not specifically pertain to these fields. One reference reports data specific to frequencies related to bone growth stimulators (Jacobson-Kram, 1997). The relevance of available biological safety research as it relates to frequencies produced by bone growth stimulators is also discussed by Bassett (1989). The evidence suggests that this type of electromagnetic energy /clinical exposure does not have adverse biological effects.

Published work on the Orthofix implantable bone growth stimulator and a developmental PEMF signal is of particular interest, considering this reclassification petition (Jacobson-Kram et al., 1997). The mutagenic potential of the electric and electromagnetic fields elicited by this device was evaluated in the Ames test, CHO chromosomal aberration assay, cell transformation assay, and unscheduled DNA synthesis. Clinical and supra clinical doses were employed and compared to untreated controls and positive controls. Measurable cell toxicity was not observed. The results indicated that the signals studied were not mutagenic nor clastogenic in these assays. Positive controls did elicit increases in these assays. The fields also did not increase cell transformation or unscheduled DNA synthesis. This report provides additional evidence that electric and electromagnetic fields do not appear to present a genetic hazard.

Bassett summarized the safety concerns of the use of PEMFs as well (1989). He noted that the PEMF energetics differ substantially from those of power lines, radiofrequency, and microwaves in that PEMFs were designed to simulate naturally occurring stress-generated electric responses. As such, PEMFs contain a selected range of frequencies and amplitudes well within the range normally presented in the body. PEMFs are asymmetric and broad-band. Predominant frequencies are at the very low end of the electromagnetic spectrum. Thus, the overwhelming amount of studies reported using other exposures do not necessarily apply to the frequencies which are the subject of this petition. Bassett describes a sarcoma model in mice which has been used as a safety screening test for new waveforms. Survival and spontaneous tumor formation in mice exposed continuously to PEMF waveforms did not differ from unexposed control animals. Overall clinical experience as reported in the existing literature does not appear to suggest a relationship between the waveforms used clinically and carcinogenesis or genotoxicity. It is prudent, however, to continue to monitor the evidence during the continued clinical experience.

Teratology

The available literature on the developmental effects of electromagnetic fields has also been reviewed recently (Juutilainen, 2005), with the emphasis on occupational and environmental exposures. The effects of radiofrequency fields (RF) electromagnetic fields and ELF electric fields have been examined in non-mammalian and mammalian species. RF fields can be teratogenic when exposure levels are sufficient to cause an increase in temperature. Frequencies of 100 MHz to 6000MHz were studied. Most commonly, 2450 MHz (microwaves) were examined. Decreased hatching, increased mortality, and functional

abnormality were observed in exposed groups when the temperature increased as a result of exposure. When the threshold maternal temperature increased, the development of rats and mice was also affected. The positive results in some studies are difficult to interpret due to study design and control issues. Limited information is available on the potential effects of prenatal exposure on postnatal behavior. No significant changes have been observed compared to the effects of positive controls.

ELF magnetic fields (50 Hz to 20KHz) have been studied fairly extensively (Juutilainen, 2005). Several attempts to duplicate studies in non-mammalian species have been performed. Abnormalities are seen in some studies in chick embryos, but results were not consistently positive or replicated. Results in fish embryos showed some delayed development, but no abnormalities. While these studies may suggest subtle effects on development, extrapolation and relevance to humans is limited. With respect to mammalian species (rats and mice), gross visceral, external, and skeletal anomalies were not observed in the reviewed studies, but there was evidence of minor skeletal alterations in several experiments. While these may be common findings in teratological studies and not always considered significant, subtle effects cannot be ruled out. This is significant is relation to the indications presented in the petition. Additional research is warranted.

Table 3. Articles on The Potential Teratologic Effects

Reference	Species/Organism	Exposure/Dosimetry	Time	Effects
Nishikawa, 1987	Pregnant mice	Bi-Osteogen System, EBI 5msec positive going burst with repetition of 15 Hz	8 hr/day between days 6th and 15th gestation 24 hr/ day days 0 – 18 of gestation	No detrimental effects on pregnancy, prenatal, postnatal effects
Bassett, 1989 *#12	Swiss Webster teratology/toxicology study > 600 Female patients (gynecologic, pregnancy, offspring histories)	PEMFs PEMFs	24hr/day for 4 generations NR	Mating, gestation, delivery, development, re-mating – no abnormalities, normal histopathology Types &rates of reproductive system disorders similar to overall population.
Landesmann and Douglas, 1990	Newts	Bi-Osteogen System 204 , EBI: 200 µsec pulse width, 28 µsec negative width, 5 msec pulse burst width with 61.24 msec between bursts.	30 days	No accelerated or inhibited limb regeneration. No affect on developmental milestones, histological analysis. Decreased number of forelimbs with a normal skeletal pattern (60%) compared to 98% in the native group and 72% in the control group. Control and PEMF group showed the same degree of abnormalities

*Included in the original reclassification search bibliography of 165 references, #Review article

In the original bibliography of 165 articles presented in the petition, one article was identified which is related to the effects pulsing electromagnetic fields on prenatal development. The Bi-Osteogen system (Electrobiology) was employed and a 5msec, positive going burst with a repetition rate of 15Hz noted. Data is provided in English, but text is in Japanese. Three experiments were conducted in pregnant mice that were exposed to PEMFs. Mice were exposed for 8 hours/day between the 6^{th} and 15^{th} day of gestation in the first experiment. In the second and third experiments, mice were exposed for 24 hours/day between 0 and 18 days of gestation. Field strength and induced voltage was determined on each floor of the housing unit. Upon sacrifice, fetuses from the first two experiments were examined for external, visceral, and skeletal anomalies. In the third experiment, the offspring were examined for behavioral development. Significant increases in the body weight of offspring was observed between 8 and 21 days, with a transient acceleration of behavioral effects. However, no detrimental effects were observed on the pregnancy or prenatal and postnatal development (Nishikawa, 1987).

Bassett also addressed the issue of teratogenesis (1989), citing the existing studies in chick embryos noted by Juutilainen and the inability to successfully reproduce the results despite careful design and control of exposure conditions. Some general growth of skeletal tissues was noted in birds, but no adverse effects on embryogenesis or development in mammals. A PEMF generator which produced pulses different that those in clinical use was reported to affect male scent-marking behavior and gonad size in rats. Exposure patterns were also different than those clinically employed. Four successive generations of mice were exposed to basic pulse patterns and no abnormalities in litter size, animal weights, behavior, or development. Neither were abnormalities of organs revealed at the termination of continuous exposure experiments. Furthermore, Bassett cites clinical experience in over 600 female patients at the time of the review documented in detailed questionnaires. This population exhibited similar data on menses, menopause, and pregnancy as the remaining female population at he time. The current literature does not suggest issues related to these types of adverse events given the clinical use of bone growth stimulators over the past 25 years.

Although not a teratology study specifically, limb regeneration of newts in response to PEMF stimulation was also studied (Landesman and Douglas, 1990). This reference appeared in the original petition bibliography. Bilateral amputations were performed on adult newts. The control group was compared with a group receiving continuous PEMF exposure (Bi-Osteogen System 204, ElectroBiology, Inc.) for 30 days, except for 30-minute feeding/watering periods twice weekly. The waveform was described as: 200 μsec pulse width, 28 μsec negative width, 5 msec pulse burst width with 61.24 msec between bursts. Both groups were maintained under identical conditions for an additional 3-4 months. Skeletal analysis was conducted on control and PEMF regenerated limbs and compared to a native group of newts. It is noted that regenerated forelimbs typically exhibit some variations in the digit and carpal bones, even without intervention. Normal regeneration does not always result in exact duplication of the previous limb in various newt species. PEMF neither accelerated nor inhibited limb regeneration. Developmental milestones and histological analysis were not affected by exposure to PEMF. There was a decreased number of forelimbs with a normal skeletal pattern (60%) compared to 98% in the native group and 72% in the control group. Both the control and PEMF group showed the same degree of abnormalities, however. There were 29/240 PEMF-exposed

limbs that showed unique gross defects (loss of digits and carpals, absence of more than one digit, excessive number of carpals, fusion of carpals, defects in the distal ends of the radius and ulna.). These types of defects have been noted also following repeated amputation and other stimuli and a common mechanism is not known.

Conclusions

Overall, the range of frequencies and exposures studied most often focus on those outside the range of interest in this petition. Generation and administration of these exposures varies. As long as temperature remains constant, the effects of the fields are negative. Increases in temperature as a result of applying the fields (thermal effect) appear to be the reason for positive effects in these assays. It is noteworthy that the available comprehensive reviews of the literature conclude that the environmental and medical exposure ranges do not appear to be genotoxic or mutagenic. Long-term bioassays also produce negative results overall. The article which specifically pertains to fields similar to those of interest in the petition adds to these negative results observed in standard genotoxicity assays. The available discussion related to the safety of PEMFs reinforces this. While the data are by no means conclusive, the evidence points to lack of genotoxic, carcinogenic, and teratologic potential of the subject waveforms. Research continues in these areas given the exposure to fields in the environment and in medical treatment.

It is also important to note that Special Controls can be utilized and have been proposed to address any potential risks. Appropriate warning language can be used. Incorporation of a warning is proposed that the long-term effects of electrical and magnetic fields have not been studied in humans. Furthermore, it should be stated that the safety and effectiveness in pregnancy have not been studied. Effects of the device on mothers and the developing fetus are not known. Anyone who is pregnant or intending to become pregnant should be referred to her physician prior to treatment (see Attachment 6).