Some non neoplastic effects of ELF magnetic fields in experimental animals

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Summary. This study has been addressed to the non neoplastic effects observed in experimental animals exposed to the ELF magnetic fields exposure, giving particular attention to the large and comprehensive data of the two-year NTP (National Toxicology Program) studies. The statistical analysis of non neoplastic incidences, whenever not presented by the study authors, has been carried out in the present study. Only the effects coherently emerging for both the animal genders have been considered; gender specific effects have obviously been separately analysed. The trend analysis has been carried out over the 4 exposure levels (0, 2, 200 μT, and 1000 μT -microTesla) and on the first 3 ones. For 28 dose-response relationships, non neoplastic effects significantly emerged (6 for hyperplasia, 4 for cyst, 4 for inflammation, 3 for focus, 3 for atrophy, 2 for cellular infiltration, and 1 for each of other 6 effects). This number is much higher than the one of neoplastic effects indicated by the NTP as significant. For many of these dose-response relationships, the trend was significant only over the first 3 treatment levels (excluding the highest one, 1000 μT/1 mT), in agreement with the results of some other studies indicating a response reduction, or even a possible anticarcinogenic effects, at considerably high exposures (mT range). The obtained results suggest a complex effect modulation pattern.

Key words: ELF, electromagnetic fields, animal experiments, non neoplastic effects.

Riassunto *(Effetti non neoplastici dei campi magnetici a frequenza estremamente bassa su animali da laboratorio)*. Questo lavoro è stato prevalentemente volto all'esame degli effetti non neoplastici associati a campi magnetici a frequenza estremamente bassa (ELF) emergenti da esperimenti su roditori, con particolare attenzione agli ampi studi del National Toxicology Program (NTP). L'analisi statistica di questi dati, qualora non presentata dagli autori degli studi, è stata effettuata nell'ambito del presente lavoro. Sono stati considerati solo gli effetti emergenti in modo coerente per gli animali dei due sessi; gli effetti specifici per uno dei due sessi sono stati ovviamente considerati separatamente. L'analisi del trend è stata effettuata per i 4 livelli di trattamento (0, 2, 200 μT, and 1000 μT - microTesla) e per i primi tre di essi. Effetti non neoplastici sono risultati a livello significativo per 28 relazioni dose-risposta (6 per l'iperplasia, 4 per le cisti, 4 per l'infiammazione, 3 per il focus, 3 per l'atrofia, 2 per l'infiltrazione cellulare, e 1 per ognuno di altri 6 tipi di effetto). Questo numero è molto più elevato di quello degli effetti neoplastici indicati dal NTP come significativi. Per molte delle citate relazioni dose-risposta il trend è risultato significativo solo per i primi 3 livelli di trattamento (escludendo quello più elevato, 1000 μT/1 mT) in accordo con i risultati di alcuni altri studi che hanno indicato un decremento della risposta o anche un qualche possibile effetto anticancerogeno per esposizioni elevate (ordine dei mT). I risultati ottenuti suggeriscono un complesso processo di modulazione degli effetti.

Parole chiave: campi magnetici, ELF, esperimenti su animali, effetti non cancerogeni.

INTRODUCTION

This study was planned with the guide of Professor Romano Zito, already reviser of its previous first phase [1], who underlined the importance of the large amount of data concerning the non-neoplastic effects of the extremely low frequency (ELF), produced by the National Toxicology Program [2] as complement of the data on neoplastic effects. At the moment, the NTP data on non neoplastic effects are the most exhaustive and comprehensive ones available. As stated by Prof. Zito, their detailed evaluation and statistical analysis, not presented in the NTP report, could provide essential information for extending the knowledge of the whole biological effects induced by ELF magnetic fields. This evaluation makes part of the present study. The final biological interpretation of these data was foreseen to be at care of Prof. Zito, but, unfortunately, this was not possible. This study is dedicated to his memory.

As known, the International Agency for Research on Cancer [3] has evaluated the extremely low-frequency magnetic fields as "possibly carcinogenic to humans" (Group 2B), based on a "limited evidence in humans

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of the carcinogenicity of extremely low-frequency magnetic fields in relation to childhood leukemia while there is inadequate evidence in humans for the carcinogenicity of extremely low-frequency magnetic fields in relation to all other cancers". Moreover, the IARC evaluated that "there is inadequate evidence in experimental animals for the carcinogenicity of extremely low-frequency magnetic fields". The US NTP [2], in the concluding remarks of its two-year lasting "Toxicology and carcinogenesis studies of 60-Hz magnetic fields in F344/n rats and B6C3F1 mice", specifies that "there was equivocal evidence of carcinogenic activity of 60-Hz magnetic fields in male F344/N rats based on increased incidences of thyroid gland C-cell neoplasms in the 0.02 and 2 G groups", while "there was no evidence of carcinogenic activity in female F344/N rats or male or female B6C3F1 exposed to 0.02, 2 or 10 G, or 10 G intermittent 60-Hz magnetic fields" [2]. In these studies, groups of 100 male and 100 female rats, and of 100 male and 100 female mice were exposed to 60-Hz magnetic fields at intensities of 0, 0.02, 2 and 10 G/ 0, 2, 200 and 1000 μT), as well as of 10 G intermittent magnetic fields (1 hour on, 1 hour off) for 18.5 hours per day, 7 days per week, 106 weeks.

At the moment, the "equivocal evidence" of carcinogenic activity of 60-Hz magnetic field in experimental animals reported by the NTP appears to be the only one not fully negative evaluation presented by an international level institution with carcinogenicity classification tasks. The NTP specifies that the "equivocal evidence of carcinogenic activity" is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be related to the agent under study. This is different from the "no evidence" that, according to the NTP, is demonstrated by studies that are interpreted as showing no agent-related increases of malignant or benign neoplasms. In the NTP two-year studies, in addition to thyroid C cell data, other statistically significant results emerge in rats and mice, in addition to thyroid C cell data, as also underlined in the IARC (2002) monograph [3]. In particular, for skin tumours, a statistically significant increase of trichoepithelioma at the 1000 μT exposure level ($p=0.029$) is reported in male rats, together with a statistically highly significant exposure-response trend for this neoplasm ($p=0.002$), and with statistically significant trends ($p=0.008$ and $p=0.018$) respectively for tricoepithelioma or basal cell adenoma, jointly considered, and for squamous cell papilloma, keratoacanthoma, thricoepitelioma, basal cell adenoma or squamous cell carcinoma, jointly considered. Lastly, a significant increase ($p=0.032$) of preputial gland carcinoma is reported for male rats. For mice, the only positive result reported is a statistically significant exposure-response trend ($p=0.032$) in males, for the adrenal cortex adenoma.

Some statistically significant decreases of neoplasm incidence in the exposed groups also emerged in the NTP studies. In particular, a significant incidence decrease is reported for leukemia in male rats and for adrenal cortex adenoma in female rats, both at the intermittent 10 G/1000 μT exposure level (respectively, $p=0.045$ and $p=0.02$). For male and female mice, a significant decrease of lung tumours is reported at the 2 G/200 μT exposure level (alveolar/bronchiolar adenoma) in male and female mice (respectively, $p=0.001$ and $p=0.002$, female mice) and at 0.02 G/2 μT in female mice ($p=0.002$). Lastly, a significant decrease of all malignant neoplasm is reported for female mice, at the 200 μT and 1000 μT exposure levels (respectively, $p=0.015$ and $p=0.024$), together with a significant negative exposure response trend ($p=0.014$). These results are interesting and will be hereafter briefly discussed.

The NTP short review of the experimental studies, available at the time of the report publication, underlines that most of them have led to negative results. In this context, skin tumor promotion experimental models have indicated either a marginal increase of skin papilloma incidence in mice with magnetic field exposure [4] or no increase in neoplasm rate [5]. In another study in mice [4], a marginal increase was observed in the number of skin tumors per tumor-bearing animals, exposed to intermittent magnetic fields. Lastly, in three different studies in mice, variable results were obtained, not supporting an effect of magnetic fields on skin tumor promotion. For rats, substantially negative studies were mentioned by the NTP [2].

More recently, the Juutilainen *et al.* [7] review has presented a comparative evaluation of the animals studies on the "cocarcinogenic effects" of 50-60 Hz magnetic fields (treatment with a genotoxic agent followed or accompanied by ELF magnetic field treatment). This analysis indicates 3 studies as positive over 14 examined, and the remaining ones as negative or not fully positive. These authors conclude that studies whose experimental design combines chronic exposure to magnetic fields with long term exposure to known carcinogens (cocarcinogenesis) are more likely suitable to produce positive effects, rather than studies based on the two step design (known carcinogen treatment followed by magnetic field treatment).

Heikkinen *et al.* [8] have effected a study on female CBA/S mice, with about 50 animals for each of 3 experimental groups, one used as "cage-control group", and the other two groups treated with ionizing radiation at the beginning of the experiment. One of these two groups was also exposed for 1.5 years (24 hours/day), at 50 Hz magnetic fields whose intensity regularly varied among 1.3, 10 and 130 μT, while the other one represented the "sham control". The authors conclude that the magnetic field exposure did not significantly increase the incidence of any primary neoplams and that, however, the observed significant increase of liver basophilic foci (25/50, exposed *vs.* 9/50, control, $p<0.001$, significance estimated in the present analysis), indicated as a probable pre-neoplastic effect in liver, is worthwhile of attention. They also report that the incidence of hepatocellular carcinomas was not significantly increased (14/50 *vs.* 7/50, $p \approx 0.07$, significance estimated in the present analysis) while no differences emerged for liver adenomas.

W. Löscher [9] has reviewed the experimental studies of the "Hannover Group" on ELF magnetic field carcinogenic activity in rats, observing that, even most of them were negative, weak or equivocal results have been mainly obtained in studies using the DMBA breast cancer model in rats (administration of 7,12-dimethylbenzo(a)anthracene – DMBA, in a single administration or repeated in prolonged period, and relatively long lasting treatment with magnetic fields). Löscher underlines that these studies, also in comparison with other ones, have pointed out some aspects of the experimental designs which, at least in part, could explain some inconsistencies emerging from different experiments on rodents. These variability causes include:

a) the rat sub-strain used in the various experiments (mentioned as the possibly most important factor in determining the effects of exposure, due to the different sensitivity of different sublines);
b) the DMBA dose (that should be sub-maximal);
c) the duration of magnetic field exposure (assuming that the magnetic fields affect tumor growth rather than tumor incidence, as Löscher hypothesises, the effects might be most easily observed early, rather than later, due to the growth progression of tumors also in control group);
d) the location of tumors in the mammary gland (due to the different sensitivity of specific parts of the organ); and lastly,
e) the flux density of magnetic field exposure, that should be in the micro-Tesla/μT range (based on the Hannover group results, which indicated a tendency of the cocarcinogenic effects of magnetic fields tend to disappear at high exposures, milli-Tesla/mT range).

In particular, the data presented by Löscher indicate the absence of significant increase of breast tumor incidence at 30 mT, while the increases at 50 and 100 μT are significant and respectively two- and three-fold higher than the one at 30 mT/30,000 μT.

As far as the magnetic field high flux density is concerned, it is also worthwhile underlining that a study by de Seze *et al.* [10] on 3 mouse strains, previously treated with carcinogenic doses of benzo(a)pyrene ("initiation") and subsequently exposed to high ELF magnetic field levels (100 mT/100,000 μT, 8 Hz, 8 hours/day, 5 days/week, from the onset of tumors to the animal death or when the tumors reached a specific level) has shown a significant decrease of tumor growth in the magnetic field-treated mice, together with a survival increase.

Moreover, a study by Tofani *et al.* [11] showed a significant tumor inhibition in nude mice subcutaneously bearing WiDr tumors (induced by a subcutaneous intercapsular injection of transformed WiDr human colon adeno-carcinoma cells) and treated with ELF and static modulated magnetic fields (70 minutes, 4 weeks), when modulated magnetic fields (modulation defined as 50 Hz fields superimposed to static fields) were used for at least the 60% of the treatment period and the average intensity was higher than 3.59 mT/3,590 μT.

An *in vitro* study by Redeva and Berg [12], on the differences induced by low frequency magnetic fields in the lethality between cancerous cells (cultured cancer cell lines) and human lymphocyte cells, has indicated that the pulsating electromagnetic fields (sinusoidal wave, 35 mT/35,000 μT peak, 50 Hz), has suggested that the combined application of such magnetic field, anticancer drugs and photodynamic therapy could be very effective.

These latter results point out that the importance of a comprehensive joint evaluation of the biological effects of ELF magnetic fields, including both the carcinogenesis studies and the studies on the possible anti-carcinogenic effects and on the possible therapeutic use of ELF magnetic fields.

The large majority of the above mentioned studies adopt an experimental design substantially different from the one of the NTP studies above discussed, which uses a two year lasting exposure to magnetic fields, without any chemical carcinogen previous or contemporary administration, in agreement with the classical carcinogenicity studies. This design is considered here particularly important, because the adopted exposure pattern is in some way most similar to typical human exposures. Moreover, this study is the most comprehensive for the number of neoplastic and non neoplastic effect types and sites examined, providing an extremely large number of data. The observation in some experimental studies of a lower carcinogenic effect or even of an anticarcinogenic effect at high ELF magnetic field levels (mT range) has been considered of main interest in the present analysis. As an example, the thyroid C-cell adenomas and carcinomas observed by the NTP are significantly increased in male rats at the intermediate exposure levels (0.02 G/2 μT and 2 G/200 μT) but not at the highest exposure level (10 G/1000 μT/1 mT), for which the increase is not significant. The same pattern arises for the thyroid C-cell focal hyperplasia in female rats *(Table 1)*.

In the previous phase of the present study [1], the thyroid C-cell data and other NTP data have been discussed. In particular, the analysis has shown that a highly significant increase of the focal hyperplasia incidence in female rats has been observed at the same exposure levels at which in male rats a highly significant increase of C-cell adenoma or carcinoma is observed and that the amounts of these increases are comparable (in the order of two-fold). As reported in the NTP study, "focal proliferative lesions smaller than five follicles in diameter are designated as focal C-cell hyperplasia, and masses larger than this are considered to be neoplasms", so that the joint consideration of thyroid C-cell hyperplasia and adenoma appears reasonable. Lastly, some increase of thyroid C-cell adenoma incidence in the exposed groups results also for female rats, even if at a non significant level, and the examination of the pooled data of thyroid C-cell adenomas or carcinomas in male and female rats still indicate a significant increase at 2 ($p=0.04$) and nearly significant ($p=0.052$) at 200 μT *(Table 1)*. These considerations suggest that female rat data may be not fully negative,

Table 1 | *Thyroid C-cell neoplasms and focal hyperplasia (data from National Toxixology Program, 1999)*

	Control	0.02 G	2 G	10 G
Thyroid C-cell, adenoma				
M rats	15/99 (15%)	25/100 (25%) p=0.035*	26/100 (26%) p=0.028*	23/100 (23%)
F rats	15/100 (15%)	20/100 (20%)	19/100 (19%)	20/100 (20%)
M + F rats	30/199 (15%)	45/200 (22%) p<0.05	45/200 (22%) p<0.05	43/200 (21%)
Thyroid C-cell, adenoma or carcinoma				
M rats	16/99 (16%) p=0.005*	31/100 (31%) p=0.009*	30/100 (30%) p=0.055*	25/100 (25%)
F rats	19/100 (19%)	22/100 (22%)	22/100 (22%)	23/100 (23%)
M + F rats	35/199 (17%)	53/200 (26%) p<0.025	52/200 (26%) p<0.05	48/200 (24%)
Thyroid C-cell, focal hyperplasia				
M rats	28/99 (28%)	22/100 (22%)	23/100 (23%)	24/100 (24%)
F rats	20/100 (20%) p<0.005	39/100 (39%) p<0.001 trend:	52/100 (52%) p<0.001	24/100 (24%) (p<0.001n)**
M + F rats	48/199 (24%)	61/200 (30%)	75/200 (37%) p=0.005 trend: p<0.001	48/200 (24%) (p<0.005n)

** Significance levels estimated by the National Toxicology Program (NTP). ** Significance levels of decrement at 10 G in comparison to the responses at 2 G or/and at 0.02 G. M: male; F: female.*

and that the thyroid C-cell effects might be reasonably assumed as affecting both the two rat genders, even at a different level.

METHODS ADOPTED FOR THE STATISTICAL ANALYSIS OF DATA

For the non neoplastic data, for which the NTP report [2] does not present a statistical analysis, the statistical significance of exposure-response trend has been evaluated in the present study with the classical Mantel-Haenszel test [13-15], without considering the 10 G (1000 μT) intermittent exposure group (qualitatively different from the other exposure groups, Control and continuous 0.02 G, 2 G, and 10 G/Control and continuous 2 μT, 200 μT and 1000 μT, which have been used by the NTP in the trend analysis, excluding the intermittent exposure group). The "*Exact Fisher test*" has been generally employed for homogeneity in incidence comparisons, also because the Chi-square test, even when appropriately usable, resulted to be somewhat less powerful then the Fisher exact test. These tests appeared to lead to results not substantially different from the ones obtained in the NTP statistical analysis.

The trends analysis effected in the present study includes both the 4 treatments (Control, 0,02 G, 2 G and 10 G/Control, 2 μT, 200 μT and 1000 μT) and the 3 first treatments (Control, 0.02 G and 2 G). This decision has been based on the above considerations about a possible response decrease in reported in various experimental animals studies for treatment levels higher than the microTesla - μT levels, and also taking into account that in the dose-response relationships (Thyroid C-cell neoplsmas) on which the NTP has based its "equivocal evidence" evaluation, is characterised by a response at 10 G (1000 μT or 1 mT) that is not significantly increased for thyroid C-cell adenomas and carcinomas in male rats, while this happens for the responses at the 0.02 G and/or 2 G treatment levels, which are sensibly higher. The trend analysis limited at the first 3 treatment levels was adopted also for testing the hypothesis of a possible lower efficiency of exposures at the 1 mT/10 G level, which is the border between the μT and mT range.

In the case of statistically significant increased or decreased incidences of an effect in one gender, the corresponding data of the other gender were also comparatively examined; the examined effect was taken into account only if the data and the trends of the two genders were compatible, as also indicated by a significance existing for the pooled data of the two genders. The number of the different dose-response relationships for the non neoplastic effects, examined and reported by the NTP is of the order of magnitude of 300 for each gender of each species. However, among them, only 60-80 dose-response relationships per gender of the two species include incidences non extremely low (higher than one or few units per one hundred), therefore consenting some appropriate statistical analysis. This reduced number is however sufficiently high to lead to the reasonable prediction that, for instance, 3 - 4 false positives could arise by chance in the case of an adopted significance level of 5%. This consideration together with the well known principle adopted by the IARC, of giving major attention to the results appearing in the two animal genders and/or in different species was the base for selecting the dose-responses hereafter presented. In particular, dose-response relationships for which incoherent trends or incoherent increases/decreases emerged in the two genders were not considered, with the obvious exception of

effects gender-specific (*e.g.*, prostate or ovary effects). Based on simple statistical principle, this criterion may be expected to remarkably reduce the above mentioned risk of false positives. Another criterion, in this case non statistical, has been the consideration of the biological reasonableness of the examined results (*e.g.*, similar effects in different tissues of the same organ).

Lastly, for completeness reasons and for avoiding selection biases, the analysis was also extended to the identification of dose-response relationships consistently suggesting an exposure-related incidence decrease of effects. In this case, also some dose-response relationship concerning neoplastic effects, presented by the NTP, has been examined.

In the *Tables 1-4*, the significance levels with an asterisk (*) are the ones estimated by the NTP, while the other ones have been estimated in the present study. The significance level of the incidence increments at the 3 exposure levels, in comparison with the control, is reported below each incidence. The significance level of the trend has been estimated up to 2 G and 10 G, and is reported below the corresponding incidences. The significance levels in parentheses, followed by the letter n (*e.g.*, p<0.01n) concern the difference (decrease) of the response to the highest exposure level (10 G) in comparison with the ones at 0.02 G and/or 2 G. This evaluation was aimed at verifying if the highest exposure level was less efficient of the lower ones in the induction of effects.

RESULTS

The analysis of the whole NTP data in non neoplastic effects indicates significant incidence increases and/or significant trends result for 28 dose-response relationships *(Table 2 and Table 3)*.

The identified significant effects include:

1) hyperplasia:
   adrenal cortex (endocrine system), in rats;
   adrenal cortex (endocrine system), in mice;
   mesenteric lymph node (hematopoietic system), in mice;
   thymus, epithelial cells (hematopoietic system), in rats;
   testes, interstitial cells (genital system), in male rats;
   ovary, rete ovarii (genital system) in female rats;
2) cyst:
   pituitary gland, pars distalis (endocrine system), in rats;
   thyroid c-cells, ultimobranchial cyst (endocrine system), in rats;
   mammary gland (integumentary system), in female rats;
   preputial gland, bilateral cysts (genital system), in male mice;
3) inflammation:
   preputial gland, chronic inflammation (genital system), in male rats;
   preputial gland (genital system), in male mice;
   prostate, acute inflammation (genital system), in male rats;
   prostate, chronic inflammation, (genital system), in male rats;
4) focus:
   liver, eosinophilic focus (alimentary system) in rats;
   liver, eosinophilic focus (alimentary system) in mice;
   liver, basophilic focus (alimentary system) in rats;
5) atrophy:
   preputial gland (genital system) in male mice;
   preputial gland, bilateral atrophy (genital system) in male mice;
   testes, bilateral atrophy (genital system) in male mice;
6) cellular infiltration:
   lung, lymphocytes (respiratory system) in rats;
   lung, istiocytes (respiratory system) in rats;
7) cytoplasmatic alteration:
   nose, olfactory epithelium (respiratory system) in rats;
8) cytoplasmatic vacuolisation:
   pancreas (alimentary system) in rats;
9) lipomatosis:
   pancreas (alimentary system) in mice;
10) hematopoietic cell proliferation:
   spleen (hematopoietc system) in mice;
11) galactocele;
12) mammary gland (integumentary system) in rats;
13) mineralization: brain, thalamus (nervous system) in mice.

The pooled incidences and dose-response relationships of the two genders for the two species have been considered as a main parameter. For gender-specific effects, only the relevant gender has been considered.

In 8 of the 28 dose-relationships reported in *Tables 2* and *3*, the trend of the pooled incidences of the two genders resulted significant over the whole 4 treatment levels. Considering also the trend over the first 3 treatment levels, the whole dose-response-relationships with a significant trend (over 4 and/or 3 treatment levels) increased up to 20.

In the same 28 dose-response relationships, a significant response increase of the two gender cumulated data, in comparison with the control, emerges 11-folds at 0.02 G/2 μT, 16-folds at 2 G/200 μT and 11-folds at 10 G/1 mT.

In 11 dose-response relationships, the incidence at the higher exposure level (10 G), resulted to be significantly lower than the ones at 0.02 G or/and 2 G. This result is coherent with the relatively low percentage of dose-responses with a trend significant over the whole 4 treatment levels and with the higher percentage of dose-response relationships with a significant trend only over the first 3 treatment groups.

The dose-response relationships resulting in some way significant for rat and mice respectively are 17 and 11.

Of the 28 dose-response relationships, 6 regard hyperplasia, 4 cyst, 4 inflammation, 3 focus, 3 atrophy, 2 cellular infiltration, 1 cytoplasmatic alteration, 1 cytoplasmatic vacuolisation, 1 lipomatosis, 1 hematopoietic cell proliferation 1 galactocele and 1 mineralization.

Among them, 17 concern non gender-specific effects (resulting in the two gender cumulated data and not only in a single gender). Other 11 dose-response re-

Table 2 | *Non neoplastic lesions: hyperplasia, cyst, inflammation, atrophy (data from National Toxicology Program, 1999)*

		Control	0.02 G	2 G	10 G
1) Adrenal cortex, hyperplasia	M rats	11/99 (11%)	15/100 (15%)	9/100 (9%)	11/100 (11%)
	F rats	11/100 (11%)	23/100 (23%) p<0.02	12/100 (12%)	8/100 (8%) (p<0.005n) *
	M + F rats	22/199 (11%)	38/200 (19%) p<0.05	21/200 (10%) (p<0.01n)	19/200 (9%)
2) Adrenal cortex, focal hyperplasia	M mice	31/99 (31%)	31/96 (32%)	38/99 (38%)	31/94 (33%)
	F mice	3/88 (3%)	8/88 (9%)	12/88 (14%) p<0.025 trend:p<0.05	9/89 (10%) p=0.068
	M + F mice	34/187 (18%)	39/184 (21%)	50/187 (27%) p<0.05 trend:p<0.05	40/183 (22%)
3) Mesenteric lymph node, hyperplasia	M mice	0/87 (0%)	7/90 (8%) p<0.01	5/96 (5%) p<0.036	1/85 (1%) (p<0.05n)
	F mice	2/83 (2%)	1/88 (1%)	4/89 (4%)	0/92 (0%)
	M + F mice	2/170 (1%)	8/178 (4%) ≈0.06	9/185 (5%) p<0.05	1/177 (0.5%) (p<0.05n)
As above, reticulum cells	F mice	3/83 (4%)	4/88 (5%)	13/89 (15%) p<0.025 trend: p <0.01	8/92 (9%)
4) Thymus, epithelial cells hyperplasia	M rats	2/97 (2%)	3/94 (3%)	3/95 (3%)	6/90 (7%) trend: p<0.05
	F rats	3/95 (3%)	1/95 (1%)	3/92 (3%)	4/91 (4%)
	M + F rats	5/192 (3%)	4/189 (2%)	6/187 (3%)	10/181 (5%) trend: p<0.05
5) Testes, interstitial cells, focal hyperplasia	M rats	8/100 (8%)	8/100 (8%)	12/100 (12%)	17/100 (17%) p<0.05 trend: p<0.025
6) Ovary, rete ovarii, hyperplasia	F rats	5/100 (5%)	14/100 (14%) p<0.05	5/100 (5%)	14/100 (14%) p<0.05
7) Pituitary gland, Pars Distalis, cyst	M rats	8/98 (8%)	6/95 (6%)	6/97 (6%)	16/100 (16%) trend: p<0.001
	F rats	21/99 (21%)	21/99 (21%)	19/98 (19%)	28/100 (28%)
	M + F rats	29/197 (15%)	27/194 (15%)	25/195 (13%)	44/200 (22%) trend: p<0.005
8) Thyroid gland, C-cells, ultimobranchial cyst	M rats	1/99 (1%)	1/100 (1%)	4/100 (4%) trend:p<0.05	7/100 (7%) p<0.05 trend: p<0.005
	F rats	2/100 (1%)	4/100 (4%)	7/100 (7%) trend: p<0.054	3/100 (3%)
	M + F rats	3/199 (1%)	5/200 (2%)	11/200 (5%) p<0.05 trend: p<0.05	10/200 (5%) p<0.05 trend: p<0.05
9) Mammary gland, cyst	F rats	47/100 (47%)	54/100 (54%)	56/100 (56%)	61/100 (61%) p<0.05 trend: p<0.05
10) Preputial gland, bilateral cyst	M mice	55/98 (56%)	75/98 (77%) p<0.005	86/100 (86%) p<0.001 trend: p<0.001	53/100 (53%) (p<0.001n)
11) Preputial gland, chronic inflammation	M rats,	18/100 (18%)	19/99 (19%)	25/100 (25%)	31/100 (31%) p<0.025 trend: p <0.01
12) Preputial gland, inflammation	M mice	15/98 (15%)	18/98 (18%)	33/100 (33%) p<0.005 trend: p<0.001	27/95 (27%) p<0.025 trend: p<0.05
13) Prostate, acute inflammation	M rats	4/100 (4%)	7/99 (7%)	15/100 (15%) p<0.01 trend: p< 0.01	7/99 (7%) (p<0.06n)
14) Prostate, chronic inflammation	M rats	6/100 (6%)	6/100 (6%)	14/100 (14%) p<0.05 trend: p< 0.025	6/100 (6%) (p<0.051n)
15) Preputial gland, atrophy	Mmice	8/98 (8%)	22/98 (22%) p<0.005	15/100 (15%)	10/95 (11%) (p<0.025n)
16) Preputial gland, bilateral atrophy	M mice	17/98 (17%)	34/98 (35%) p<0.01	34/100 (34%) p<0.01	27/95 (28%) p<0.05
17) Testes, bilateral atrophy	M mice	0/99 (0%)	2/98 (2%)	0/94 (0%)	6/96 (6%) p<0.025 trend: p<0.005

** Significance levels of decrement at 10 G in comparison to the responses at 2 G or/and at 0.02 G. M: male; F: female.*

Table 3 | *Non neoplastic lesions: Focus, cellular infiltration, cell proliferation, cytoplasmatic alteration, cytoplasmatic vacuolization, lipomatosis, mineralization, galactocele (data from National Toxicology Program, 1999)*

		Control	0.02 G	2 G	10 G
1) Liver, eosinophilc focus	M rats	21/100 (21%)	19/100 (19%)	26/100 (26%)	17/100 (17%)
	F rats	18/100 (18%)	24/100 (24%)	30/100 (30%) p<0.05 trend: p<0.05	24/100 (24%)
	M + F rats	39/200 (19%)	43/200 (21%)	56/200 (28%) p<0.05 trend: p<0.025	41/200 (20%)
2) Liver, eosinophilc focus	M mice	10/100 (10%)	12/100 (12%)	11/100 (11%)	14/100 (14%)
	F mice	5/98 (5%)	3/97 (3%)	10/98 (10%) trend: p<0.025	10/99 (10%) trend: p=0.05
	M + F mice	15/198 (8%)	15/197 (8%)	21/198 (11%)	24/199 (12%) trend: p=0.05
3) Liver, basophilic focus	M rats	35/100 (35%)	35/100 (35%)	47/100 (47%) p=0.06 trend: p<0.05	37/100 (37%)
	F rats	66/100 (66%)	82/100 (82%) p<0.025	77/100 (77%)	66/100 (66%) (p<0.025n)*
	M + F rats	101/200 (50%)	117/200 (58%) p≈0.07	124/200 (62%) p<0.025 trend: p<0.05	103/200 (51%) (p<0.05n)
4) Spleen, hematopoietic cell proliferation	M mice	37/99 (37%)	43/98 (44%)	52/98 (53%) p<0.025 trend: p<0.025	36/93 (39%) (p<0.025n)
	F mice	74/91 (81%)	77/93 (83%)	87/95 (92%) p<0.05 trend: p<0.025	83/93 (89%)
	M + F mice	111/190 (58%)	120/191 (63%)	139/193 (72%) p<0.01 trend: p<0.005	119/186 (64%) (p<0.07n)
5) Lung, cellular infiltration, lymphocytes	M rats	0/100 (0%)	11/100 (11%) p<0.001	5/100 (5%) p=0.03	2/100 (2%) (p<0.001n)
	F rats	1/100 (1%)	6/100 (6%)	4/100 (4%)	7/100 (7%) p=0.032
	M + F rats	1/200 (0.5%)	17/200 (8%) p<0.001	9/200 (4%) p<0.01	9/200 (4%) p<0.01
6) Lung, cellular infiltration, histiocytes	M rats	8/100 (8%)	18/100 (18%) p<0.025	12/100 (12%)	6/100 (6%) (p<0.01n)
	F rats	31/100 (31%)	42/100 (42%)	34/100 (34%)	46/100 (46%) p<0.05 trend: p<0.05
	M + F rats	39/200 (19%)	60/200 (30%) p<0.025	46/200 (23%)	52/200 (26%)
7) Nose, olfactory epithelium, cytoplasmatic alteration	M rats	36/100 (36%)	32/100 (32%)	48/100 (48%) trend: p<0.05	41/100 (41%)
	F rats	69/100 (69%)	83/100 (83%) p<0.05	87/100 (87%) p<0.005 trend: p<0.025	74/100 (74%) (p<0.05n)
	M + F rats	105/200 (52%)	115/198 (58%)	135/200 (67%) p<0.025 trend: p<0.005	115/200 (58%) (p<0.05n)
8) Pancreas, cytoplasmatic vacuolization	M mice	16/99 (16%)	31/99 (31%) p<0.01	28/98 (29%) p<0.05	5/95 (5%) (p<0.005n/ p<0.001n)
	F mice	12/87 (14%)	21/94(22%)	18/96 (19%)	16/94 (17%)
	M + F mice	28/186 (15%)	52/193 (30%) p<0.005	46/194(25%) p<0.025	21/193 (11%) (p<0.001n)
9) Pancreas, lipomatosis	M mice	1/99 (1%)	11/99 (11%) p<0.005	14/98 (14%) p<0.001 trend: p<0.01	1/95 (1%) (p<0.005n)
	F mice	21/87 (24%)	16/94 (17%)	23/96 (24%)	29/94 (29%) trend: p<0.05
	M + F mice	22/186 (12%)	27/193 (14%)	37/194 (19%) p<0.05 trend: p<0.03	30/189 (16%)
10) Brain, mineralization	M mice	70/100 (70%)	68/99 (69%)	60/100 (60%)	79/100 (79%) trend: p<0.05
	F mice	47/99 (47%)	68/100 (68%) p<0.005	55/98 (56%)	60/98 (61%) p<0.05
	M + F mice	117/199 (59%)	136/199 (68%) p<0.05	115/198 (58%)	139/198 (70%) p<0.025 trend: p<0.05
11) Mammary gland, galactocele	M rats	0/99 (0%)	2/97 (2%)	5/100 (5%) p=0.03 trend: p<0.025	2/100 (2%)
	F rats	10/100 (10%)	7/100 (7%)	14/100 (14%)	7/100 (7%)
	M + F rats	10/195 (5%)	9/197 (5%)	19/200 (9%) p≈0.07 trend: p<0.025	9/200 (4%) (p≈0.05n)

** Significance levels of decrement at 10 G in comparison to the responses at 2 G or/and at 0.02 G. M: male; F: female.*

lationships concern gender-specific effects (4 for male and 1 for female rats, and 5 for male mice for genital system, 1 for female rats for mammary cyst).

Ten dose-response relationships concern the genital system (2 for preputial gland inflammation, 2 for preputial gland atrophy, 1 for preputial gland cyst, 2 for prostate inflammation, 1 for testes interstitial cell hyperplasia, 1 for ovary, rete ovary hyperplasia, 1 for testes atrophy), 5 the alimentary system (3 for liver eosinophilic or basophilic focus, 1 for pancreas cytoplasmatic vacuolisation, 1 for pancreas lipomatosis), 4 the endocrine system (2 for adrenal cortex hyperplasia, 1 for cyst of pituary gland, pars distalis, 1 for cyst of thyroid C-cell), 3 the hematopoietic system (for mesenteric lymph node hyperplasia, for thymus epithelial cell hyperplasia, for spleen hematopoietic cell proliferation), 3 the respiratory system (for lung cellular infiltration, lymphocytes, for lung cellular infiltration, istiocytes, for nose olfactory epithelium cytoplasmatic alteration), 2 the integumentary system (mammary gland cyst – only female rats –, mammary gland galactocele), and 1 for nervous system (for mineralization, brain thalamus).

The dose-response relationships for which resulted significant treatment-related response decreases are reported in *Table 4*, also including neoplastic effects with this pattern. This evaluation appeared useful for both the completeness of the analysis and for taking into account the high significant response decreases resulting by NTP evaluation, in particular for lung alveolar/bronchiolar adenomas. For non neoplastic effects, the present analysis indicated the preputial gland cyst (only in male mice) and the bilateral pigmentation of kidney renal tube as worthwhile of attention. The cases including non coherent decreases or negative trends in the two genders were not considered, following the same criteria adopted for the positive results reported in *Tables 1*, *2* and *3*.

DISCUSSION

A first observation is that the number of non neoplastic effects, resulting in some way statistically significant, is remarkably higher than the very low number of the significant carcinogenic effects identified by the NTP and already cited in the introduction. This also means that the non neoplastic effects, comprehensively studied and reported by the NTP, provide very important information, not available at this completeness level from other studies.

In 9 of the analysed dose-response relationships, the responses to the intermediate treatment levels that are significantly increased in comparison with control (at 0.02 G/2 μT and/or at 2 G/200 μT) result also significantly higher than the ones to the most elevated treatment level (10 G/1000 μT/1 mT), and, in other 6 cases, are sensibly higher, even at a non significant level. A similar condition also exists for the dose-response relationship of thyroid C-cell tumors in male rats, on which the NTP evaluation of "equivocal evidence" was based, and also clearly results for the thyroid C-cell focal hyperplasia in female rats (whose dose response is fully similar to the one of tumors in male rats) *(Table 1)*.

As discussed in the introduction, Löscher has indicated the μT range as the most appropriate for carcinogenicity testing of ELF magnetic fields in experimental studies as the ones carried out by the "Hannover" Group (cocarcinogenesis, DMBA and ELF treatments).

Table 4 | *Dose-response relationships with dose-related response decrease*

		Control	0.02 G	2 G	10 G
1) All organs, malignant neoplasm	M mice	40/100 (40%)	49/100 (49%) p=0.134*	45/100 (45%) p=0.302*	49/100 (40%) p=0.103*
	F mice	55/100 (55%)	58/100 (58%) p=0.448*	39/100 (39%) p=0.015n*	40/100 (40%) p=0.024n*
	M + F mice	95/200 (47%)	107/200 (53%)	84/100 (84%)	89/100 (89%)
2) All organs, malignant or benign neoplasms	M mice	71/100 (71%)	81/100 (81%) p=0.081*	72/100 (72%) p=0.547*	74/100 (74%) p=0.343
	F mice	78/100 (78%)	80/100 (80%) p=0.561*	72/100 (39%) p=0.237n*	71/100 (71%) p=0.193n*
	M + F mice	149/200 (74%)	161/200 (80%)	144/200 (72%)	145/100 (72%)
3) Lung, alveolar/bronchiolar adenoma	M mice	26/100 (26%)	11/99 (11%) p=0.007n*	9/100 (0%) p=0.001n* trend: p<0.025n	16/99 (16%) p=0.077n*
	F mice	9/95 (9%)	6/100 (6%)	0/99 (0%) p=0.002n* trend: p<0.005n	5/99 (5%)
	M + F mice	35/195 (18%)	17/199 (8%) p<0.01	9/199 (4%) p<0.001n trend: p<0.001n	21/198 (11%)
4) Preputial gland, cyst	M mice	29/98 (30%)	13/98 (13%) p<0.01n	7/100 (7%) p<0.001n trend: p<0.001n	23/95 (24%)
5) Kidney, renal tube, bilateral pigmentation	M rats	29/100 (29%)	20/100 (20%)	26/100 (26%)	23/100 (23%)
	F rats	26/100 (26%)	11/100 (11%) p<0.025n	13/100 (13%) p<0.05n	30/100 (30%)
	M + F rats	55/200 (27%)	31/200 (15%)	39/200 (19%)	53/100 (26%)

** Significance levels estimated by the National Toxicology Program (NTP). M: male; F: female.*

Other studies, above mentioned, mainly addressed to a possible therapeutic use of ELF magnetic fields, have indicated the mT exposure range as possibly leading to some decrease of some tumor growth rate (at levels over some mT). Therefore, the hypothesis that 1 mT (1000 μT/10 G) could represent the level at which the carcinogenic and toxic effects may initiate to decline, seems reasonable at least for some effects.

The non neoplastic effects resulting in some way significant may be regarded in the light of some neoplastic effects, indicated by the NTP as significant or close to a significant level.

For instance, as above mentioned, a significant incidence increase is reported by the NTP in male rats for preputial gland carcinoma at 2 G/200 μT, while the incidence at the other remaining treatment groups is always null. The data in *Table 2* indicate for this organ a significant increase of cyst (male mice at 0.02 and 2 G), of inflammation (male mice, at 2 and 10 G) and chronic inflammation (male rats, at 10 G), and of atrophy (simple and bilateral) at more treatment levels in male mice.

The only significant increase of carcinogenic effects reported for male mice by the NTP is a positive trend ($p=0.032$) for the adrenal cortex adenomas. A significant increase of focal hyperplasia of adrenal cortex emerges for the cumulated data of male and female mice and of male and female rats respectively at 2 G and at 0.02 G treatment levels *(Table 2)*.

The NTP study separately reports the incidences of adenomas and bilateral adenomas of testes in male rats, as well as the incidences of the focal hyperplasia and bilateral focal hyperplasia of interstitial cells of testes. The incidences in male rats of testes interstitial cell adenomas (non-bilateral) are characterised by an increasing trend close to significance ($p \approx 0.06$) and by an incidence increase at 10 G also close to the significance ($p \approx 0.06$) (11/100 at control; 17/100 at 0.02 G; 19/100 at 2G; and 20/100 at 10 G), as estimated in the present study. The interstitial cell focal hyperplasia of testes in male rats (considered separately from the bilateral one) appears to be characterised by a similar and significant trend ($p<0.025$) and by a significant increase at 10 G ($p< 0.05$) *(Table 2)*. In male rats, for both the bilateral adenomas and the bilateral focal hyperplasia of testes, the incidences are much higher, without significant differences. The NTP report indicates for male mice very low incidences (in the order of 1%-2%) of neoplasms of testes, without any significant difference; the only significant non neoplastic effect in testes, emerging for male mice in the present analysis, is some increase of bilateral atrophy at 10 G ($p<0.05$) *(Table 2)*, while for the simple atrophy (non bilateral) no significant difference emerge (the large majority of the reported incidences is in the range of <1%-3%).

As far as the mammary gland carcinoma is concerned, the incidence increase in female rats, reported by the NTP is a 7/100 response at 0.02 G, compared to a 2/100 for control ($p=0.098$, as estimated by the NTP), within a dose-response relationship of 2/100, 7/100, 5/100 and 2/100 (respectively for control, 0.02 G, 2 G and 10 G, with the response to the highest treatment lower than the ones at 0.02 and 2 G). In male rats, the only non null incidence is 1/97 (1%) at 0.02 G. Pooling the female and male incidences, a response of 2/199 is obtained for the control and of 8/197 at 0.02 G, with a significance level of $p<0.055$. The incidence of mammary gland cyst in female rats appears to be significantly increased at 10 G, with a significant trend up to this level *(Table 2)*. It is worthwhile mentioning that positive effects for mammary tumors have been found in some other studies.

The incidence of liver eosinophilic foci is significantly increased in both rats and mice, while the incidence of basophilic foci is significantly increased only in rats. The liver neoplastic effects reported by the NTP in rats are substantially absent (incidences null or the order of 1%, and only in one case, of 2%). For male and female mice, the analysis by the NTP indicates no significant differences among the incidences of neoplastic effects on liver. For liver effects, it is worthwhile mentioning that a significant increase of liver basophilic foci together with a non significant increase of liver hepatocellular carcinomas resulted in the above cited initiation/promotion study by Heikkinen *et al.* [8]; in the conclusions, the authors specify that the overall results do not provide evidence of a carcinogenic effects of 50 Hz magnetic fields, although the liver changes may warrant further evaluation.

The incidences of hematopoietic neoplasms reported by the NTP for rats are generally null and at most at 2% level; similar results, even if with values slightly higher, are reported for mice; as a whole, no significant differences are reported. Therefore, the non neoplastic effects resulting significant in the present analysis (lymph nodes, hematopoietic cell proliferation) *(Table 2 and 3)* seem to be the only ones significantly emerging for the hematopoietic system.

Significant effects for skin neoplasms are reported by the NTP in male rats (as above mentioned in the introduction), for trichoepitelioma (significant increase at 10 G, with a highly significant trend up to this level) and for a set of various skin tumors, jointly considered (trichoepitelioma, squamous cell papilloma, keratoacanthoma, basal cell adenoma or squamous cell carcinoma, with a significant trend up to 10 G). For female rats, the NTP reports an incidence increase of a set of skin tumors (trichoepitelioma, squamous cell papilloma, keratoacanthoma or basal cell adenomas) at 2 G ($p=0.064$, as estimated by the NTP, with a trend significant up to this level – $p<0.025$ –, as estimated in the present analysis: 1/100 at control; 2/100 at 0.02 G; 6/100 at 2 G; 1/100 at 10 G). Skin tumors increases have been found in some of other studies, so that this result is worthwhile of attention. Based on the present analysis, non neoplastic skin effects emerge at a significant level only for the mammary gland, while this does not happen for other skin lesions (the incidences mostly are null or ≤1%-2%, without any significant difference).

The NTP study has pointed out some dose-response for which the trend is negative or some responses are significantly lower than the control; these data are

important. For instance, for the neoplastic effects on lungs, it is worthwhile noticing that the NTP reports for male mice a highly significant incidence decrease of lung alveolar/bronchiolar adenomas at 0.02 G and 2 G for male mice (respectively, 11/99 and 9/100 *vs.* 26/100-control, p=0.007 and p<0.001), and, for female mice, a highly significant decrease at 2 G (0/99 *vs.* 9/95-control, p=0.002). The analysis effected in the present study on the pooled male and female data clearly confirms the highly significant incidence decrease at 0.02 and 2 G reported in the NTP analysis, and, moreover, indicates a highly significant negative monotonic trend over the first 3 treatment levels (up to 2 G) *(Table 4)*. The consistency of these effects in the two genders indicates that is difficult to attribute them simply to chance. For rats, no significant differences are reported in the NTP analysis of lung alveolar/bronchiolar adenoma or of lung alveolar/bronchiolar adenoma or carcinoma (the highest incidence variation is 7/100 at 0.02 G *vs.* 3/100 for control, p=0.145 as reported by the NTP). For non-neoplastic effects, the analysis carried out in the present study indicates in rats a significant increase of cellular infiltration in lungs (lymphocytes and histiocytes), more significant at 0.02 G *(Table 3)*.

A significant incidence decrease is also reported by the NTP for the malignant tumors of all organs in female mice at 2 G and at 10 G (respectively, 39/100 *vs.* 55/100-control, p=0.015; and 40/100 *vs.* 55/100, p=0.024, NTP estimates). For male mice, however, a slight non significant incidence increase results for the 3 treated groups, as shown in *Table 4*, and the pooled incidences of male and female mice do not indicate any significant difference or trend. Moreover, the incidences reported by the NTP for malignant and benign tumors for all organs indicate an incidence increase at 0.02 G for male mice (81/100 *vs.* 71/100-control, p=0.081, as estimated by the NTP, and for female mice, 80/100 *vs.* 78/100-control). The analysis of the pooled data of the two genders indicates incidences of 74%, for control, 80% at 0.02 G) and 72% at 2 G and 10 G, with no significant differences.

The NTP discussion of these latter data gives most attention to the incidence decreases of lung tumors rather than to the other observed incidence decreases. The above discussion is fully in agreement with this.

Lastly, in *Table 4* the dose-response of cyst of preputial gland is reported and the one of the bilateral pigmentation of kidney renal tube. The first one, even non confirmed by male rat data (for which this effect is substantially absent – only one non null incidence, 1% at 2 G), is characterised by a high significance of the response decrease at 0.02 G (13/98 *vs.* 29/98-control, p<0.01) and, in particular, at 2 G (7/100 *vs.* 29/98-control, p<0.001) and by a highly significant negative trend up to this level, p<0.001). The incidence at 10 G is not significantly different from the one of control.

For the pigmentation of the renal tube of kidney, the control incidences result very close in the two genders (29/100 and 26/100). This suggests that the incidence decreases at 0.02 G and at 2 G in comparison with the control are difficult to be simply attributed to a control high incidence resulting by chance. Moreover, the incidence decrease for the pooled data of the two genders is highly significant.

In any case, however, the decrease of lung tumours appears as the sounder one, at least from the statistical point of view.

CONCLUSIONS

The large number of non neoplastic data produced by the NTP two year studies are of great value for an overall evaluation of the biological effects of ELF magnetic fields. Moreover, the selection of the exposure range (up to 10 G/1000 μT/1mT) appears very appropriate, because it includes the levels (μT range) at which adverse effects have been mostly observed in other studies, according to some recent evaluations. The analysis here effected indicates that a relatively high fraction of the examined dose-responses of non neoplastic effects is characterised by a significant trend up to 2 G/200 μT but not by a significant trend up to 10 G/1000 μT. However, this is not a general result; in fact, in a minor percentage, effects emerge at this latter exposure level, so that its inclusion remains important. The above discussed hypotheses of a lower incidence of some adverse effects or, even, of the possible existence of anticarcinogenic effect above 1 mT, provide some confirmation to this finding. In any case, this result suggests that the absence of trend significance up to 1 mT should not necessarily imply the absence of effects, in particular if the trend is significant up to 200 μT exposure level.

As a whole, non neoplastic effects emerged at a significant level much more frequently than neoplastic effects. Their analysis allowed in some cases to insert some neoplastic findings in a suitable and informative context. It may be also useful to remind that the study by Heikkinen *et al.* (2001), including the examination of more than 30 non neoplastic effects, has pointed out a highly significant increase of basophilic focus incidence in female mice liver, considered as a possibly preneoplastic effect, while no significant results emerged for the about 30 neoplastic effects examined, including, however, a non significant 2-fold increase of liver carcinoma.

This analysis points out that various non neoplastic effects may be associated to ELF magnetic field exposure in the 0-10 G intensity range. Some of these non neoplastic effects may provide information useful to better evaluate the neoplastic ones, and provide further support to "the marginal increase of neoplasms that may be related to the agent under study", on which the "equivocal evidence" is based.

As a whole, this analysis suggests that ELF magnetic fields could have some complex modulation capability of carcinogenic and non carcinogenic effects, including in more cases an effect increase but, under specific conditions (*e.g.*, high exposure levels and/or for specific end points) also some effect decrease.

"In conclusion, it may be reasonably assumed that the biology of carcinogenic risk of magnetic fields is a largely uncharted domain, demanding much work and time to be elucidated. The present polemics dividing science in two opposite fields, one of them denying any appreciable carcinogenic effect of magnetic fields, and the other one hypothesising their dramatic effects, are presently devoid of reliable and exhaustive scientific support, which could only be provided by further research" (R. Zito, 2003) [1].

Acknowledgements

The Authors wish to tank Giovanni Riva for his contribution in information retrieval.

Submitted on invitation.
Accepted on 10 April 2006.

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