The evaluation and management of potential adverse human health effects associated with exposure from physical and chemical agents within our environment is a fundamental responsibility of public health agencies around the world. Beginning with the advent of AM broadcast towers in the early 1900’s, followed by FM radio and TV towers in the late 1930’s / early 1940’s, our level of exposure to radio frequency (RF) emissions has steadily increased. Within the last 15 years, an explosive proliferation of mobile phones and other wireless technologies, coupled with an increasing social awareness of health-related issues, has lead to an element of concern by some regarding potential adverse effects on human health associated with long-term low-level RF exposure. The World Health Organization (WHO) has taken a lead in developing an agenda to direct the formation of a necessary and sufficient research database on their website at http://www.who.int/peh-emf/en/. A hazard evaluation is scheduled to be performed by the International Agency for Research on Cancer (IARC) in 2005 / 2006 to determine if long-term RF exposure can act as a carcinogen. A similar evaluation is scheduled for later 2006 / 2007 by the WHO to determine if RF exposure is associated with any non-cancer adverse health effects. From these hazard evaluations, public health officials can identify and manage potential risks within a given population and environment by making informed decisions on policy and practice.

A second major element necessary in any successful hazard evaluation is a clear definition of what constitutes a hazard. Correlations between significantly toxic and carcinogenic agents and adverse effects on human health can often be made with a high degree of certainty, however the converse is rarely (if ever) true. It is, in fact, impossible to completely prove that exposure to any agent poses a “zero” risk to an entire population of people; even with an infinite amount of research one can never prove the null hypothesis. As the degree of hazard associated with exposure to an agent decreases, the distinction between a small level of risk and no risk becomes blurred and a matter of semantics. Humans have a fairly significant baseline level of genetic deterioration and spontaneous adverse health effects that must be considered, and in fact some of the most essential physical and chemical elements in our environment (namely oxygen, sunlight, and water) act as the major culprits. This, in effect, relegates hazards below the spontaneous threshold as somewhat inconsequential and arbitrary in terms of their actual risk. Related to this issue, scientific research using biological
systems is itself limited by the background level of spontaneous adverse events as well as the threshold for detection of these events using conventional biological assays. The difference between a small valid effect, a baseline variation, or an experimental artifact can quickly become difficult to distinguish. Finally, an endless number of hypothetical possibilities involving "susceptible" individuals with as yet uncharacterized genetic or behavioral attributes making them more sensitive than the majority of the population can always be hypothesized, but can never be fully addressed. Under the strictest of definitions, almost every physical or chemical agent in the environment will pose some level of risk to human health. Such an interpretation clearly negates the utility of human health hazard evaluations. There is a logical position to be taken that a level of hazard need not be defined to the order of six sigma (approximately 3 events in a million) for a definitive conclusion to be reached. Further, evaluations cannot be expected to account for every hypothetical synergistic interaction, genetic predisposition, or behavioral idiosyncrasy that may exist within a given population. There must be a point where one can confidently determine that an agent is simply not a significant hazard, and thus poses no significant risk to human health.

A process for evaluating chemical and physical agents for carcinogenicity has been defined by IARC. Presently, 885 agents have been evaluated and placed into one of five categories:

1. Carcinogen (88 agents)
2a. Probable carcinogen (64 agents)
2b. Possible carcinogen (236 agents)
3. Unclassifiable (496 agents)
4. Probably NOT a carcinogen (1 agent)

The evaluation process appropriately places emphasis on human data (epidemiology), and secondarily relies on animal data when human data are weak or nonexistent. In vitro data are used only as supportive evidence of a mechanism when health-related effects have been demonstrated in human or animal studies.

While the choice of agents selected for evaluation is obviously based upon varying degrees of prior suspicion, concern, or predisposition as a cancer causing, there is a clear pattern that can be discerned from previous hazard evaluations. Only 10% of the agents have demonstrated "sufficient evidence of a positive association with cancer in studies where chance, bias and confounding can be ruled out with reasonable confidence" to place them in category 1. A few have demonstrated "limited evidence of a positive association between exposure and cancer for which a causal relationship is considered credible, but chance, bias or confounding cannot be ruled out with reasonable confidence" to place them in category 2b. Finally, only a single agent has met the requirements of "lack of carcinogenicity, including several adequate studies covering the full range of levels of exposure that are mutually consistent in reporting a lack of positive association between exposure and cancer (although the possibility of a very small risk at the levels of exposure studied can never be excluded)" to place it in category 4. Such placements in categories 1, 2a, and 4 are helpful in offering policy guidance to government health officials. In contrast, category 2b contains approximately one quarter of the agents, and is defined ambiguously as "inadequate evidence in humans, but sufficient evidence in experimental animals to suggest possible carcinogenicity" offering little practical guidance other than blind precautionary avoidance. The remaining agents (over half) are given a completely uninformative classification (category 3).

It is entirely understandable that pressure exists on any hazard evaluation team, especially knowing their assessment may be used to direct policy and position regarding risk of exposure for entire populations. However, placing agents in ambiguously defined categories to insure avoidance of type 2 error (false negative) does little in the way of offering practical guidance. Such a pattern could ultimately render the entire process ineffective and result in more confusion than clarification. It should be possible for a hazard evaluation team to assess a reasonable body of evidence and confidently categorize an agent as being either "probably carcinogenic" or "probably not carcinogenic". Although in vitro data can be helpful from a basic science perspective to elucidate mechanisms, such studies should not prevail over adequate epidemiologic and/or animal data to re-categorize an agent into an ill-defined category for precautionary reasons.
Previous expert review panels formed to evaluate RF exposure, including The Royal Society of Canada, U.S. FDA, U.S. FCC, Australian Committee on EM Energy & Public Health Issues, Japanese Ministry of Post and Telecomm., Korean Ministry of Comm., New Zealand Ministry of Health & Environ., Singapore Health Sciences Authority, Austrian Ministry for Health and Consumer Protection, German Federal Office for Radiation Protection, France Commission for Consumer Safety, Netherlands Ministry of Health and Well-Being, and UK National Radiological Protection Board, WHO, International Commission on Non-Ionizing Radiation Protection, European Commission Expert Group, and the U.K. Independent Expert Group on Mobile Phones, have unanimously concluded that no credible evidence exists that RF exposures within accepted (non-thermal) limits cause any adverse health effects. However, many of these expert panels have also stated to varying degrees that additional research is needed and that precautionary steps are appropriate, leaving the overall conclusion of each report weakened and open to wider interpretation.

The current RF research database consists of over 1330 published studies on the effects of exposure to humans, animals, and cell cultures in vitro. Many additional studies are ongoing and scheduled for completion by the time the IARC hazard evaluation is performed. This is compared to the handful of epidemiologic and animal studies available for the vast majority of other agents evaluated (http://monographs.iarc.fr/). Specifically, over 50 epidemiologic reports assessing cancer endpoints from RF exposure in case control and cohort populations exist. The majority are negative, although there are some reports of positive correlations. The positive reports largely come from studies of residential proximity to broadcast towers or exposure from occupational sources where individual dose assessment is absent, group dose assignments are loosely defined and prone to wide variability, and control of other confounding factors in the residential or work environment is limited. Although a greater number of studies with similar design report no effect, a more telling indication is the lack of consistent cancer endpoints from one positive study to another, even when study populations and RF sources are similar. In thirteen epidemiologic studies looking at mobile phone exposure (where RF dose is localized and significantly higher than broadcast tower and previously examined occupational sources), reports are predominantly negative. The largest and most comprehensive of these studies by Johansson et al examined a cohort of 420,000 mobile phone subscribers in Denmark and reported no effect over several cancer endpoints (J Natl Cancer Inst, 2001, 93:203-206). Of two studies reporting associations with tumors, these are inconsistent in the actual tumor endpoint identified. Hardell et al first reported no correlation with brain tumors (Int J Oncol, 1999, 15:113-116), although after statistical re-evaluation reported an increase in benign (but not malignant) tumors with analogue phone exposure, as well as a correlation with laterality (Eur J Cancer Prev, 2001, 10:1-7; Eur J Cancer Prev, 2002, 11:377-386; Int. J. Rad. Biol., 2002, 78:931-936). In contrast, Auvinen et al reported no laterality effect, and a slight increase in malignant (but not benign) brain tumors (Epidemiology, 2002, 13:356-359), but cautioned that their findings were not definitive. Subsequent to the Auvinen report, Hardell performed additional statistical re-evaluation and reported increases in both benign and malignant brain tumors from their original study group data (Neuroepidemiology, 2003, 22:124-129; Int. J Oncology, 2003, 22:399-407). These results are not supported by laterality or tumor data from several other large studies of mobile phone exposure including Muscat et al (Neurology, 2002, 58: 1304-1306; JAMA, 2000, 284:3001-3007), Inskip & Linet (N Engl J Med, 2001, 344:79-86), Johanson et al (2001), and Kahn et al (Irish Med J, 2003, 96(8): 240-2). A current multi-national case control study involving 13 different country sites and administered by IARC is scheduled for completion in 2004 / 2005. The epidemiologic studies reported to date plus the additional IARC studies should provide ample data to enable a definitive hazard evaluation of RF exposure.

With regard to animal studies, again the RF database is replete with reports. Twelve long term animal bioassays using RF exposures ranging from 2 to 23 hours per day for up to two years and at levels ranging from a few mW/kg to that approaching the limit for significant tissue heating have all reported no association with a battery of tumor and pathological endpoints. Nine additional studies
are currently ongoing to address the effects of mobile phone and emerging wireless technology exposures. Fifteen studies using chemically, radiation, or genetically initiated animal models have reported no effect of RF exposure on promoting cancer. Of the two studies that have reported an effect (Repacholi et al, Radiation Research (1997) 147(5):631-640; Szmigielski et al, Bioelectromagnetics (1982) 3(2):179-191 & Arch Dermatol Res (1982) 274(3-4):303-312), independent replication has failed to verify the finding, and additional independent replication currently ongoing and will be available for the IARC 2005/2006 evaluation. Finally, two studies of tumor cell line injection have shown no effect of non-thermal levels of RF exposure (Salford & Persson, Bioelectrochem & Bioenerget (1993) 30:313-318; Higashikubo et al Radiation Research (1999) 152:665-671).

Over 200 completed or ongoing in vitro studies are listed in the RF research database. Endpoints such as DNA & chromosomal damage have some relevance to risk analysis and are either negative or efforts to verify initial positive reports by independent replication in another laboratory have failed. Most other in vitro studies report sporadic and inconsistent findings over a wide array of endpoints that cannot be directly tied to a human health effect. As such, their utility in a risk evaluation, especially in light of the current abundance of epidemiologic and animal study data, is questionable.

**Summary**

It is the responsibility of public health officials to perform hazard evaluations that are as accurate, definitive, and timely as possible so potential human health risk factors can be accurately identified and managed. This is achieved initially by directing the assembly of an appropriate research database. Before hazard evaluation begins, it is essential to clearly define "hazard" in terms of its relative effect in humans. In performing a logical evaluation of the available research, it is essential to distinguish between studies that provide data relevant to human health endpoints versus those reporting innocuous, irrelevant, or un-interpretable biological effects. Of the studies reporting on relevant parameters, these must be taken together to construct a clear picture of consistent responses. Priority with regard to the weight of a study within the hazard evaluation should be assigned following the IARC guidelines, namely epidemiological studies followed by animal studies and finally in vitro studies for the purpose of deciphering mechanisms for previously determined effects. In addition, the weight of a study should also depend upon the demonstration of independent replication in another laboratory under similar conditions to verify the results, especially if the results deviate or contradict other published reports in the literature. This is true for both positive as well as negative findings.

When all these issues are considered for RF, the possibility for definitive hazard evaluation appears promising. Clearly, the available RF research database is much larger than any chemical or physical agent predecessor and continues to grow. While a number of studies included in the research database digress from the WHO agenda, there exist an ample number of studies satisfying the necessary requirements, especially with regard to epidemiologic and animal studies. Evaluation of the RF research database by numerous expert review panels has already resulted in a consistent conclusion of no credible evidence for an adverse health effect, however subsequent precautionary verbiage in each report has usually weakened this position to some extent and implied that a legitimate concern or indication exists for as yet undetermined adverse health effects. It is of the utmost importance that upcoming hazard evaluations be definitive, either substantiating or refuting an association between RF exposure and an adverse health effect, especially in light of the relative wealth of material available for evaluation and the implications for wireless technologies that have quickly become a fixture in our culture and can be anticipated to completely innervate our global society in the near future.