Comments from Annie J. Sasco, MD, MPH, SM, DrPH, former Unit Chief at IARC-WHO and former Director of Research of the *INSERM* (French NIH), Bordeaux, France

These comments are made as a private citizen or a citizen of the world but my education and professional experience give further credibility to my words.

I am a physician and a scientist having spent most of the past 35 years working on the epidemiology of cancer. I graduated as an MD'78 from the University of Bordeaux, France, also getting several specialized qualifications (hygiene and social medicine, occupational medicine, spatial and aeronautical medicine, sociology). I successfully completed 3 degrees at the Harvard School of Public Health: Master of Public Health'79, Master of Science in Biostatistics and Epidemiology'80 and Doctor of Public Health in Epidemiology, Biostatistics and Evaluation'86. While being a Harvard Teaching Fellow for a few years I joined the *INSERM* (French NIH) and worked while on secundment from *INSERM* at the International Agency for Research on Cancer – World Health Organization (IARC-WHO) for 22 years, including 9 as Head of Programme and then Chief of Unit of Epidemiology for Cancer Prevention and 2 as Acting Chief of the WHO Programme for Cancer Control. I later returned to an *INSERM* Research Unit at the University of Bordeaux.

Over the decades, my focus switched from behavioral to environmental risk factors as I was confronted by the huge increase in cancer occurrence worldwide, not only in terms of burden of disease, but also in incidence rates after due consideration to the changes in population size and age structure. As these increases cannot be linked to genetic changes, nor only to behavioral modifications, and after taking into account the role of screening, earlier detection, improvement in diagnosis and better registration of cancer, increases in the occurrence of many cancers in different parts of the world have to be recognized as a true fact. The most logical potential explanation of these increases is the change in our environment in the past 50 to 70 years. Although carcinogens always existed, the presence of chemical and physical carcinogens in the air we breathe, the water we drink, the food we eat and objects of daily leaving exploded. While I recognize the exact quantification of the attributable role of these contaminants in cancer occurrence remains debatable, I contend it is scientifically arguable a non neglectable part may be due to these pollutants. One of the most ubiquitous exposures to physical agents is the exposure to Radio Frequency Radiations (RFR) which has been one of the most rapidly expanding, in particular over the past 30 years and this is accelerating. Soon the exposure to RFR will be so widespread that it will be almost impossible to find unexposed human populations and human epidemiology will face an unprecedented challenge.

The NTP experimental study on exposure of rats and mice to RFR very nicely complements what is already known from the epidemiology of cell phone use. Although epidemiology is often presented as showing limited evidence of carcinogenicity, my contention is that most epidemiological studies and in particular case-referent studies while finding no overall increased risk when comparing exposed to unexposed humans do find increased risk in the group where it is expected to be found, namely the "most heavily exposed", whatever the exact definition is, varying from study to study. This is the case of the Hardell studies in the Nordic countries, the INTERPHONE international study and the CERENAT study in France. Such a consistent finding should not be attributed to chance, but rather should be seen as what one can expect, especially with a relatively short study period for what was a new exposure. In that context, the NTP study brought additional evidence on the carcinogenicity of RFR in experimental animals.

Most of the questions I had while reading the preliminary report were answered during the 3 day meeting last March which I had the opportunity to attend in person and where I presented public oral comments. I was exceedingly satisfied to follow all exchanges and discussions and to note 7 separate evaluations were strengthened in terms of the scale of evidence for carcinogenicity (2 from some evidence to clear evidence, 3 from equivocal evidence to some evidence and 2 from no evidence to some evidence). In addition the expert panel voted unanimously the recognition that the exposures studied increased several non neoplastic lesions, in particular in the heart, brain and endocrine organs.

I truly want to congratulate the External Peer Review panel for these upgrades, which I fully support. The criteria described in the definition of the levels of the evidence of carcinogenic activity as used in the Technical Report were met for the upgrade to be accepted. In addition, I want to outline, one more time, the fact that the tumors which have been demonstrated as increased in the exposed rats are from a histopathological point of view the tumors which are also seen in exposed humans. The best example corresponds to the schwannoma seen in the heart in rats and in the acoustic nerve in humans, probably because the rats experienced whole body exposure whereas humans using a cell phone hold it close to their ear. The fact that rats developed glioma as humans do in also worth underlying. Finally the general pattern of equivocal evidence for all endocrine organs studied should not be overlooked. The level of evidence was even considered as some evidence for the adrenals. These effects point to an endocrine-disrupting mechanism which should be further evaluated and may explain why some of the dose-effects were non linear.

The next two paragraphs address both the report but also the new document on follow-up studies on RFR that I read on line on June 1st, 2018. I want to state that I support the document submitted by Dr Michael Wyde and the need for studies on perinatal effects of *in utero* exposure as well as non cancer end points which are also pertinent to human health. In addition, I want to elaborate on two suggestions I already made in my March comments, which are not considered, yet, in the June document:

- For future studies, it could be advisable to have an unexposed group larger than each of the exposed ones, in order to build in a more stable reference population and thereby avoid the pitfalls of using historical controls, in particular for rare tumors or other rare outcomes. Larger studies will turn out more statistically significant results which are considered by many as an important criteria of evaluation. My own position is to argue that in any event statistical significance is just one aspect of evaluation of the relation between exposure and disease. Biological significance and concordance of results between humans and animals clearly reinforce the strength of the evidence of carcinogenicity.

- Along the same line, may I offer for consideration the proposal that in addition to looking at dose-response on one hand and pair-wise comparisons (a test for each exposure level *versus* the non exposed) on the other hand, one should also consider a simple and straightforward comparison of unexposed *versus* all exposed taken as one group (if needed with the introduction of a control variable for dose assignment). The sheer fact of having larger numbers in the exposed group will lead to more results being statistically significant. All exposed animals, taken as one group, independently of the exposure level to which they were assigned, developed more tumors than unexposed animals for a number of examined sites and this should not be ignored. Given that survival was lower in unexposed rats, comforted by the fact that survival was lower than in historical controls, suggestion had been made also by some other people than myself that a proper statistical analysis with due correction for survival when looking at the overall tumor burden in exposed *versus* non exposed rats could have been carried out. These types of analysis should be very seriously considered for incorporation into the protocol of studies to be done in the, hopefully near, future.

My conclusion will somewhat change compared to the one I wrote last March. Almost 10 years ago, Dr David Servan-Scheiber and myself co-wrote what is known as the 20 doctors and scientists appeal (Paris, France, June 2008), calling on people to use their cell phones in a cautious way. We considered at that time there was already enough evidence to advise people to recommend 10 simple measures to follow: when calling, keep their phone as far away from their body as they could; use the loud speaker; keep conversations short; switch to the use of a corded landline when possible or send text-messages rather than talk; avoid any use of cell phone by children and young adolescents; keep the phone away from the bed or turned off at night; when not in use avoid carrying the phone directly on your body or in your pocket and in particular for pregnant women; change side when talking and avoid using the phone when the reception is poor; choose a phone with the lowest SAR; try to stay at a distance from people using cell phones, in particular in closed settings such as cars, trains or elevators.

Since the NTP results were put in a Report and since the March meeting, many institutions and groups, including within NIEHS, and all over the world, do now recommend these precautions to be taken when using a cell phone. The population is finally getting more and more knowledgeable about cell phones and this is excellent. Does this mean the job is done? Sure not, because exposure of human populations to radiofrequency radiations is just getting worse and worse by the day and on an unprecedented scale. Whereas one can decide not to use a cell phone or to exert caution while using it, the environmental sources of exposure are covering the world. Development of 5G technologies will be launched at the level of many cities on an "experimental" basis. This experiment is being carried out on humans, not on rats and mice, whereas the study of these frequencies and intensities of exposure have not yet been properly addressed in laboratory animals. Should this be allowed? Should the launching of hundreds more satellites around the earth to leave no zone unaccessible to Internet be done? Do we have the answer? I consider that we now have enough evidence for discussing prevention rather than just precaution for cell phones. For other devices, do we need to wait years and years more to try to have results from almost impossible to carry out studies to conclude one apparatus by apparatus: are wifi routers carcinogenic? Are cell towers carcinogenic? Are smart meters carcinogenic? Are smart watches carcinogenic? When the IARC Monograph was published, the conclusion stood for RadioFrequency ElectroMagneticFields exposure, not just for cell phones. This was wise because this is the exposure we have to worry about, not the apparatus delivering it. For these other sources, and while carrying out proper experimental assessment, let us continue to take action in the name of the precautionary principle as we call it now, including in the Constitution of some countries. After all, it is just the new name of the old Hippocratic oath "*Primum non nocere*" (First, do no harm). Some industries and multinationals may have some big money to be lost in the short term (while waiting for evidence of safety?) but isn't this a good price to pay for the health of the populations of the world?

My last words will be exceedingly practical to state the importance for the health of all populations in the world to have independent agencies carrying out the work of evaluating agents. This cannot be left to the industries themselves to evaluate their own products, neither to academics in the best known institutions doing the job for the industry, openly or under cover. Conflicts of interest have to be looked for and taken into account. It is absolutely crucial a US institution such as the NIEHS remains clear of undue political pressure or influence of powerful multinationals. The same applies to international institutions and in particular to the IARC. I worked there for 22 years and I still closely follow what happens. In the past, the IARC has been accused to be too close to the interests of the industry. Nowadays, IARC is accused of being too sensitive to the preoccupations of environmentalists. In fact, from the inside and from the outside, I am convinced that the IARC and in particular the Monograph programme did an excellent job and did contribute to save millions of premature deaths in the world in the past decades. IARC is even more than ever before needed to provide unbiased evaluation of carcinogenicity in a way no other institution is capable of doing it. Therefore the idea of cutting funding for the NIEHS as well as for IARC if it is acted on will lead to irreversible damage to the health of all populations and in particular the most vulnerable. It is unacceptable and unethical. Only with sufficient funding will the NIEHS be able to do what to Dr Wyde stated in the document he submitted on line for the June meeting "Additional studies will have the potential to expand to newer, current technologies and those evolving technologies that will become the new standard in the telecommunications industry." This is most urgent.