SYNERGIES AND RFR SAFETY LIMITS

by

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This document examines the role of synergies in setting of safety limits.

WHAT ARE SYNERGIES

Synergies are one outcome of effects from the combination of multiple stimuli. In our book chapter on the health effects of non-ionizing radiation combined with other stimuli

(http://stip.gatech.edu/wp-content/uploads/2017/03/371048_1_En_4_Chapter_OnlinePDF.pdf)

we defined four types of combination effects:

Additive effects (the combined effect of two or more agents acting in the same general direction approximates the sum of the effects of the agents administered separately, subject to the maximum possible effects in biological systems);

Antagonistic effects (the combined effects of two agents acting in different/ opposite directions are smaller than the effect of any one of them in standalone mode);

Potentiative effects (the increased effect of an agent by concurrent action of another agent that does not have a stand-alone effect); and

Synergistic effects (the combined effect of two or more agents is significantly greater than the sum of the effects of each agent administered alone, subject to the maximum possible effects in biological systems).

WHY ARE SYNERGIES IMPORTANT

Synergies have *conceptually* similar effects on 1) treatments for diseases and 2) contributing factors to diseases. For treatments, usually, synergies allow less of each component (in a combination of stimuli) to be used for effectiveness compared to the levels obtained when examining the effectiveness of each component in isolation (aka single stressor experiment). For contributing factors, usually, synergies allow less of each component to cause damage compared to the levels obtained when examining the effectiveness of each component in isolation.

Thus, when setting safety/exposure limits for contributing factors in particular, safety/exposure limits for a given synergy component based on results from experiments in isolation (single stressor) could be substantially higher than the levels at which that component could cause damage when used in combination with the other synergy components.

WHAT ARE SOME EXAMPLES OF SYNERGIES IN BIOMEDICINE

I did a quick search for all types of synergies in Medline (not restricted to synergies that include RFR), and retrieved many thousands of records. Appendix 1 presents a few examples of contributing factor synergies, with RFR being present in some of the synergies.

Items 1-3 are the most interesting, in my estimation. In these cases, each of the items tested in isolation was essentially benign (in the parameter range selected), yet in combination contributed to harmful effects. Depending on where each substance in isolation starts to show damaging effects, ***the difference in setting safety limits based on experiments in isolation (single stressor experiments)and based on the actual experiments in combination could be substantial***.

Items 4-7 are probably reflective of most contributing factor synergies reported in the biomedical literature from laboratory experiments. Some modest damage is shown by each component of the combination in isolation (in the parameter range selected), but the synergy of the combination enhances the damage substantially.

Items 8-10 are combinations that include RFR, and they are of the general type identified in items 4-7. Note that all the combinations shown so far consist of two items. This is typical of lab experiments reported in the literature. Combinations of more than two items in lab experiments are relatively rare, for reasons that will be provided later.

Item 11 is the same type as items 4-7, but reflective of an interesting application.

Items 12-13 reflect an interesting combination of stimuli, sunlight and a potentially toxic stimulus. Sunlight, in appropriate amounts, can be viewed as foundational to good human health. It is probably the best source of Vitamin D through its stimulative effect on the skin. Yet, in recent years, sunlight has developed a reputation as potentially harmful, even in less than overly strong doses.

These two examples show that the skin can become overly sensitive to UV radiation through ingestion of, or exposure to, substances that can act as photosynthesizers. This combination of sunlight and one or more photosynthesizers can increase the risk of certain types of skin cancer.

Some of the substances that directly increase this photosynthesizer effect can be identified from simple laboratory experiments. What combinations of other substances that, by themselves, do not act as photosynthesizers, will produce a synergetic effect resulting in enhanced photosynthesizing? Or, what combinations of substances that, by themselves, have been shown to be weak photosynthesizers, will result in a strong photosynthesizing effect due to synergy?

Sunlight, a human health requirement, may not be the culprit here, at least in many cases not involving overexposure or predisposition. The culprit may be the combinations of other potentially toxic stimuli (to which we are exposed) that result in a strong photosynthesizing effect. Of course, it benefits the industries responsible for producing these potentially toxic stimuli to shift the blame for skin cancers to sunlight, since they can continue to produce these toxins unabated.

Item 14 addresses multi-component mixtures. The two takeaways are 1) the synergistic effects predominated at lower effect levels, and 2) the relevance of synergistic effects increase with the complexity of the mixture. So, the greater the number of components, the more important the synergies, and the lower the levels of some or all of the components required to cause damage.

Therefore, even the effects of combinations of two contributing factors found in laboratory experiments may provide insufficiently protective safety/exposure limits, compared to the effects of larger combinations characteristic of the real world.

CELL TOWERS/CELL PHONES AND SYNERGIES

The epidemiological studies on cell towers and cell phones reflect the real-world synergies, although many of the constituent contributing factors to the synergy remain unknown. For higher accuracy in these types of studies, one would have to instrument the test subjects for (at a minimum) measuring the major and semi-major contributing factors 24/7 over many years. This would include the RFR contributing factor, but also potential contributing factors from the chemical, physical, biological, and psychological worlds.

The cell tower results, imperfect as they are, show increasing cancer incidence starting in the low thousands of microwatts/square meter. Contrast this with the recent NTP and Ramazzini results of RFR in 'isolation', which show statistically significant increases in cancer starting in the millions of microwatts/square meter. And, most of the cell tower studies don't measure actual indoor exposures, so ***the actual power fluxes experienced by the residents could be an order of magnitude less for many of the residents in the so-called danger zone within a few hundred meters of the cell tower***.

DIFFICULTIES IN SIMULATING REAL-WORD SYNERGIES INCLUDING RFR

The reason few combinations are selected for study derives from combinatorics. Consider the number of possible combinations of two and three items. For n variables, and possible combinations of a subset of n consisting of r variables, the number of combinations is: C(n,r)=n!/(r!*(n-r)!), where [!] denotes the factorial function. For large n, and r small compared to n, $C(n,r)\sim=n^r/r!$ For large n, C becomes a large number. How large? Consider the following.

It would be useful to identify comprehensively those substances that could combine with RFR to produce synergetic adverse health effects. There are many tens of thousands of items that could be potential candidates for study. Is there any way to narrow those down?

My book 'Pervasive Causes of Disease'

(https://smartech.gatech.edu/handle/1853/53714)

examined contributing factors to ~4,000 diseases, and identified factors that contributed to 1) any of these diseases and 2) a threshold number of diseases. On the order of 800 substances that contributed to at least a threshold number of the ~4,000 diseases were identified. These 800 pervasive causes constituted about ten percent of the total number of causes (90% of which impacted less than the threshold number of diseases) identified for the ~4,000 diseases. The total number of causes identified for all diseases (~8,000) might be a good starting point for identifying additional potential AD causes. Why is this a reasonable assumption?

The various systems in the body are inter-related. The immune system, neural system, endocrine system, circulatory system, etc, are linked. There are research disciplines devoted to study of these linked systems (e.g., neuroimmunology, neuroimmunoendocrinology, etc). Most of the ~8,000 causes impacted one or more of these inter-related systems. Many of the studies focused on the impact of the test substance on (typically) one system only. It would be reasonable to expect that a substance impacting one of the systems above would have some level of impact on the other systems above, with some impacts being more significant than others.

Thus, the ~8,000 potential causes would be candidates for evaluation as RFR partners. However, many of these ~8,000 potential contributing factors are relatively rare in the existing biomedical literature. Their rarity may be because 1) they are 'weak' contributing factors, 2) they have not yet been studied for

many diseases, or 3) they may have been suppressed from publication by the sponsor or journal. Let's examine two sub-sets of this 8,000 total initially. Assume the top 1,000 contributing factors are reasonably important (essentially those deemed 'pervasive' in my book), and assume the top 100 contributing factors are quite important. How many experiments would be required to examine their synergies with RFR comprehensively?

1. 1000 contributing factors as possible RFR partners

If all possible combinations of the 1000 contributing factors were partnered with RFR, there would be 1000! [factorial] experiments required. The number is essentially infinite. We will examine combinations starting at the other end of the combinatorial spectrum.

For potential synergies of RFR combined with ***one*** other contributing factor, 1000 experiments would be required to cover all 1000 contributing factors. And, each experiment would be more complex than an experiment for each component in isolation. For example, suppose four values were selected for each variable. In the simplest illustrative case, the isolated experiment would require four runs for each variable. In the combination experiment, sixteen runs would be required.

For potential synergies of RFR and ***two*** other contributing factors (a three component synergy), ~500,000 experiments would be required (according to the approximate formula above). An online calculator gives the exact number as 499,500, so the approximation is quite reasonable.

For potential synergies of RFR and ***three*** other contributing factors (a four component synergy), 166,167,000 experiments would be required. Given the cost and time of e.g. the NTP experiment, the number of two, three, or four component synergy experiments required to cover all 1000 possibilities is completely unrealistic.

2. 100 contributing factors as possible RFR partners

For potential synergies of RFR combined with ***one*** other contributing factor, 100 experiments would be required to cover all 100 contributing factors. For potential synergies of RFR and ***two*** other contributing factors (a three component synergy), 4,950 experiments would be required. For potential synergies of RFR and ***three*** other contributing factors (a four component synergy), 161,700 experiments would be required. Even RFR and one other contributing factor require a large number of experiments, and the two and three other contributing factor scenarios are again completely unrealistic in terms of number of experiments and available resources required.

3. 10 contributing factors as possible RFR partners

We consider the additional case of combinations of ten contributing factors with RFR. For potential synergies of RFR and ***one*** other contributing factor, 10 experiments would be required to cover all 10 contributing factors. For potential synergies of RFR and ***two*** other contributing factors (a three component synergy), 45 experiments would be required. For potential synergies of RFR and ***three*** other contributing factors (a four component synergy), 120 experiments would be required. While these numbers are still huge, based on the experience with the NTP study, they are not out of the realm of possibility.

THE ROLE OF SYNERGIES IN SETTING RFR SAFETY LIMITS

It is clear from the above analysis that RFR in combination with other potential disease contributing factors needs to be studied and used as the basis for setting of credible RFR safety limits. Additionally, safety limits for the non-RFR members of the combination should be re-examined for the impact of RFR on their potential for damage.

In fact, the objective function should be to maximize safety of the combination, since what will cause damage to real people in the real world are combinations of contributing factors. This requires a global optimization (on the combination) rather than a local optimization (on any single constituent). A broader global optimization over all potential combinations would ensure maximal protection for the public.

In the ideal situation for optimization over each combination, we would set a safety target for the combination (e.g., less than X cancers per 10,000, and/or changes in selected biomarkers less than Y%, etc). We would then adjust the safety/exposure limits on each constituent using an iterative process until the target has been met.

The practical question becomes how do we select the combinations for optimization, and how many combinations do we choose for purposes of approximating the true global optimization? As we have seen, the potential number of combinations to which one could be exposed is enormous. The true global optimization would cover all possible combinations!

It is unclear at this point exactly how the optimization, the iterative procedure, and the combinations selection would be done. There is a discipline called Cumulative Risk Assessment (see Appendix 2 for an Abstract of a paper outlining this process) that purportedly takes account of what they call multiple stressors. It's by no means clear from the paper exactly how they would address a situation of the scale enumerated above in the previous section on combinatorics.

ALTERNATIVE APPROACHES TO IDENTIFY SYNERGISTIC EFFECTS

It is also clear that the present laboratory approach will hardly scratch the surface of what is required to generate a comprehensive picture of the potential real-world damage from RFR, given the real-world limitations imposed by combinatorics.

Even in the best realistic case of tens or maybe even hundreds of combinations of two or three contributing factors being run in the next few years, we are still left with the simulation issues I mentioned in a previous email: full-body deep-penetration, different species (hopefully, the high power density levels will have decreased substantially in these combination runs). So, what alternatives exist to generate useful results for RFR safety/exposure limit setting?

Since much of the present flurry of RFR opposition activity is being driven by the ongoing acceleration of 4G/5G small cell tower infrastructure implementation, I'll focus on cell towers. For the past three decades, we have in fact been running a massive experiment where a significant number of human beings are exposed to RFR for much of the day, with some exposed all of the day. Many people have unwittingly been serving as 'guinea pigs' in this experiment, and probably the majority of participants have not given ***'informed consent'***. In the world of research, this is known as unethical research!

This massive experiment is the construction and operation of hundreds of thousands of cell towers in the USA alone, resulting in exposure of many people to substantial amounts of wireless radiation. The vast majority of these cell towers are located in residential and commercial areas. The few studies that have been done on the adverse health effects of living in close proximity to these towers barely scratch the surface of what is possible. While the results from these studies are alarming because of the increased incidence of cancer (for those in close proximity) they present, the studies do not identify all the contributing factors combined with the RFR nor control the variables in any way similar to the laboratory experiments.

People throughout the USA (and the world) have exposures to myriad contributing factors with different exposure times and different exposure intensities. Without people being instrumented 24/7 with

massive numbers of sensors to measure these temporal exposure patterns, we have little idea of these temporal exposure 'signatures' for any individual, and don't really know what synergies with RFR are operable for any individual.

Despite these data deficiencies, the different cell tower studies arrive at similar conclusions. Cancer incidence starts to increase at cell tower power fluxes on the order of 1000-2000 microwatts/square meter (three orders of magnitude less than shown in the recent NTP and Ramazinni isolated RFR exposure studies), and cancer incidence starts to increase within about 400-500 meters of the antenna. There tends to be a latency time of a few years before the cancers appear, as one would expect.

It seems clear to me this database should be augmented with supporting data, and 'mined' to the full extent. In particular, we would do a nationwide study of health effects of people living in the proximity of cell towers. We would ensure the cell towers examined are representative of many different types of locations and people. We would provide the residents (or occupants, for commercial buildings near cell towers) questionnaires similar to those proposed for diagnostics in our recent Alzheimer's Disease reversal paper

(https://smartech.gatech.edu/handle/1853/59311).

We would provide a list of potential contributing factors, and the respondents would provide some idea of their exposure to these contributing factors. They would also be asked to supply their medical history, including the timing of significant health changes. In parallel, we would instrument their house rooms/office rooms to measure RFR power flux trajectories over time. The final result would provide a comprehensive (albeit imperfect) picture of the adverse impacts of existing cell towers on health. It would incorporate all operable synergies by default, although the details of many of these synergy components would remain unknown.

Unfortunately, such an undertaking, even with Manhattan Project urgency, would take years. Under present circumstances, hundreds of thousands of small 4G/5G cell towers would be installed during that period.

WHO SHOULD PERFORM THESE STUDIES

The only organization with sufficient resources (of all types) to perform these studies (especially the cell tower studies with potential privacy and other issues) is the Federal government. Unfortunately, as we have seen with the passage of the Telecommunications Act and subsequent Executive, Legislative, Regulatory, and Judicial decisions, the Federal government has acted as the Agent of the telcoms rather than the American people.

This problem is not limited to RFR regulation. My JDIS paper presented examples of Federal regulatory agencies serving as effective Agents of myriad industries in suppressing studies showing adverse effects of their products. An interesting example on water fluoridation excerpted from my JDIS paper is shown in Appendix 3. **Note the players involved!**

The Federal government has allowed this massive RFR exposure experiment (with much of the American public serving as guinea pigs) to be performed without provision of ***'informed consent'***. Many citizens have supported construction of these cell towers without having been informed by the government of their potential dangers.

Why would we entrust the Federal government to perform these large RFR synergy experiments; why would their incentives and motivations to advance the interests of the telecoms over those of the American public be different? The issue of who would sponsor and oversee the research needs to be resolved before we can expect believable and credible results to be produced.

CONCLUSIONS

Combining potential disease contributing factors with RFR reduces the levels of RFR power flux associated with disease. Studies that include these synergies are necessary for credible RFR safety limit setting.

This document has presented two approaches for obtaining this synergy data: lab animal (typically rodent) experiments with 'tight' controls on the RFR and contributing factor exposures, and cell tower epidemiological studies on health effects associated with exposures to contributing factors. The former approach has limitations based on species differences, penetration depth differences, and sheer numbers of experiments required to approach the combinations reflective of real-world synergies. The latter approach has limitations based on not knowing the full 'signature' of exposures of each individual to potential disease contributing factors.

Both approaches are useful. The former approach can provide relative impacts of adding contributing factors and observing the decrease in RFR threshold dose required to initiate serious diseases. It could also provide insight to biological mechanisms. The latter approach can show macro-level results of the adverse impacts of many contributing factors, even though the details of some of these contributing factors are unknown.

As we have seen with the handful of cell tower health impact studies already reported, the power flux thresholds for cancer incidence, the cell tower proximity extent for cancer incidence, and the latency periods for cancer incidence are relatively similar. A more detailed and comprehensive cell tower study as suggested above would offer further weight to these previous findings, and offer new insights as well.

The results from either group of studies will take years to produce. If we continue along our present path, hundreds of thousands of new small cell towers will have been installed during that research period. The damage will have been done by the time the results are produced. We need a moratorium on new cell tower construction until such results have been obtained.

EPILOGUE

I have not done any surveys to determine what fraction of toxic stimuli have exposure limits determined mainly by 1) experiments in isolation and 2) experiments that include combinations of toxic stimuli. It is my impression (from reading thousands of abstracts relating to discussions and recommendations of exposure limits) that most of these experiments involve one 'stressor' in isolation (single stressor experiments). It is also my impression, from having read many thousands of synergy papers across many substances and diseases, that synergetic effects are ubiquitous across contributing factors and their impacts on disease. Therefore, ***single stressor experiments as the main determinants for safety/exposure limits may be insufficient for human health protection from these potentially toxic contributing factors.***

It should be obvious to the reader that any Exposure Limits/Safety Limits depending in part or in whole on experiments run in isolation (single stressor experiments) will probably produce Exposure Limits that are ***above the level where significant adverse health effects begin to appear***. We would not know the magnitude of the gap between Exposure Limits that strongly depend on single stressor results and Exposure Limits that would result from comprehensive potentially toxic stimuli combination studies until these combination studies have been conducted and the effects of their synergies identified. ***There is no reason to believe a priori that this gap would not be large for many potentially toxic stimuli.***

In other words, there is no reason to believe today that ANY of the Exposure Limits on potentially toxic stimuli that have been set by ANY of the regulatory agencies are protective against serious adverse health effects. Some Exposure Limits may be relatively more protective than others due to safety factors being incorporated and studies beyond single stressor being incorporated in the final determination, but none have the full evidentiary base to inspire high levels of confidence in protection.

We will never be able to obtain a true global optimization over all potential combinations of potentially toxic stimuli to minimize adverse synergetic effects. However, it is imperative to go beyond the first-order approximation of single stressor experiments for setting Exposure Limits. Higher-order approximations afforded by combined stressor experiments will provide more realistic Exposure Limits for damage control.

APPENDIX 1 - EXAMPLES OF SYNERGIES IN BIOMEDICINE

The format of these examples is the title of the paper in quotes ("") followed by (typically) a quoted sentence or two from the abstract in parentheses ().

1. "Synergistic Toxicity Produced by Mixtures of Biocompatible Gold Nanoparticles and Widely Used Surfactants."

(These mixtures produced synergistic toxicity at concentrations where the individual components were benign.)

2. " Synergistic action of the nephrotoxic mycotoxins ochratoxin A and citrinin at nanomolar concentrations in human proximal tubule-derived cells. "

(Only concurrent but not individual exposure to OTA and CIT at nanomolar concentrations led to (i) an increase of TNF protein and mRNA, (ii) a decrease of COX-2 protein and mRNA, (iii) a decrease of E-cadherin protein and (iv) an increase of vimentin and alpha-SMA protein.)

3. " DNA damage in rat lymphocytes treated in vitro with iron cations and exposed to 7 Mt magnetic fields (Static Or 50 Hz). "

(Lymphocyte exposure to MF at 7 mT did not increase the number of cells with DNA damage in the comet assay. Incubation of lymphocytes with 10 mug/ml FeCl2 did not produce a detectable damage of DNA either. However, when the FeCl2-incubated lymphocytes were simultaneously exposed to 7 mT MF the number of damaged cells was significantly increased and reached about 20% for static MF and 15% for power frequency MF.)

4. "Concurrent administration of diethylhexyl phthalate reduces the threshold dose at which bisphenol A disrupts blastocyst implantation and cadherins in mice."

"Stress lowers the threshold dose at which bisphenol A disrupts blastocyst implantation, in conjunction with decreased uterine closure and e-cadherin"

5. "Synergistic toxicity of zno nanoparticles and dimethoate in mice: Enhancing their biodistribution by synergistic binding of serum albumin and dimethoate to zno nanoparticles "

(Although nano ZnO was low toxic to mice, coexposure to nano ZnO and DM significantly enhanced DM-induced oxidative damage in the liver.)

6. " Adverse effect of combination of chronic psychosocial stress and high fat diet on hippocampus-dependent memory in rats."

(DTC value for above groups indicated that chronic stress or HFD, alone, resulted in a mild impairment of spatial memory, but the combination of chronic stress and HFD resulted in a more severe and long-lasting memory impairment.)

7. "Neurotoxicity induced by methamphetamine-heroin combination in PC12 cells"

(These results suggest that the combination of METH and heroin is more neurotoxic than either drug alone)

8. " The effect of 900 and 1800MHz GSM-like radiofrequency irradiation and nicotine sulfate administration on the embryonic development of Xenopus laevis "

(However, the combined effects of GSM-like RF-EMR and NS on Xenopus embryos were more severe than the effect of RF-EMR or NS alone.)

9. " Mobile Phone Use, Blood Lead Levels, and Attention Deficit Hyperactivity Symptoms in Children: A Longitudinal Study "

(The results suggest that simultaneous exposure to lead and RF from mobile phone use was associated with increased ADHD symptom risk)

10. "Tumor promotion by exposure to radiofrequency electromagnetic fields below exposure limits for humans"

(The exposure devices consisted of eight radial waveguides with 16 cages each, arranged in stacks of two and connected to power amplifiers and RF-generators.....At day 14 p.c., the females in the exposure devices were injected (i.p.) with ethylnitrosourea (ENU).....at a dose of 40 mg/kg in saline.....Numbers of tumors of the lungs and livers in exposed animals were significantly higher than in sham-exposed controls. In addition, lymphomas were also found to be significantly elevated by exposure)

11. "Impaired ecosystem process despite little effects on populations: modeling combined effects of warming and toxicants"

(Our results suggest that exposure to the same amount of toxicants can disproportionately compromise ecosystem processing depending on global warming scenarios; for example, reducing organismal feeding rates by 50% will reduce resource processing by 50% in current temperature conditions, but by up to 200% with warming of 4 degrees C.)

12. " Photosensitizing Agents and the Risk of Non-Melanoma Skin Cancer: A Population-Based Case-Control Study"

(Certain commonly prescribed photosensitizing medications may enhance the risk of developing SCC [squamous cell carcinoma], especially in individuals with a sun sensitive phenotype, and may increase the risk of developing BCC [basal cell carcinoma] and incidence of BCC at a younger age.)

13. " Occupational syncarcinogenesis in the skin - combined effects of two carcinogens from the German occupational disease list "

(Following adequate cumulative occupational exposure to natural UV light as well as occupational exposure to polycyclic aromatic hydrocarbons, NMSC or its precursor lesions arising in UV-exposed areas should be reported.....in terms of syncarcinogenesis".)

14. "The synergistic toxicity of the multiple chemical mixtures: Implications for risk assessment in the terrestrial environment"

(In four-component and five-component mixtures, the synergistic effects predominated at lower effect levels, while the patterns of interactions found in six, seven, and eight-component mixtures displayed synergism..... the relevance of synergistic effects increase with the complexity of the mixture.)

APPENDIX 2 - CUMULATIVE RISK ASSESSMENT PAPER (2015)

Title

Aggregate Exposure and Cumulative Risk Assessment--Integrating Occupational and Non-occupational Risk Factors.

Abstract

Occupational exposure limits have traditionally focused on preventing morbidity and mortality arising from inhalation exposures to individual chemical stressors in the workplace. While central to occupational risk assessment, occupational exposure limits have limited application as a refined disease prevention tool because they do not account for all of the complexities of the work and non-occupational environments and are based on varying health endpoints. To be of greater utility, occupational exposure limits and other risk management tools could integrate broader consideration of risks from multiple exposure pathways and routes (aggregate risk) as well as the combined risk from exposure to both chemical and non-chemical stressors, within and beyond the workplace, including the possibility that such exposures may cause interactions or modify the toxic effects observed (cumulative risk). Although still at a rudimentary stage in many cases, a variety of methods and tools have been developed or are being used in allied risk assessment fields to incorporate such considerations in the risk assessment process. These approaches, which are collectively referred to as cumulative risk assessment, have potential to be adapted or modified for occupational scenarios and provide a tangible path forward for occupational risk assessment. Accounting for complex exposures in the workplace and the broader risks faced by the individual also requires a more complete consideration of the composite effects of occupational and non-occupational risk factors to fully assess and manage worker health problems. Barriers to integrating these different factors remain, but new and ongoing community-based and worker health-related initiatives may provide mechanisms for identifying and integrating risk from aggregate exposures and cumulative risks from all relevant sources, be they occupational or non-occupational.

APPENDIX 3 - EPA/NTP STUDY ON HEALTH EFFECTS OF WATER FLUORIDATION

I will close with an example from my JDIS paper

(http://manu47.magtech.com.cn/Jwk3_jdis/10.20309/jdis.201623)

of one component in the determination of the safety of fluoridation. it appears this was a single stressor study. When we take into account this study, the FCC Exposure Limit guidelines, the safety determinations from some of the other studies in my JDIS paper, and the vast literature on the under-reporting of adverse events in the biomedical literature, a very troubling picture begins to emerge.

In my JDIS paper, I presented the example of EPA's addressing safety limits of fluoridation (p.19). I summarized the issue as follows: "Dr. William Marcus was a toxicologist and Senior Science Advisor at EPA. He reported potential cover-up of cancers (***by the National Toxicology Program***) resulting from fluoride ingestion (Interview, 1995), and was fired in 1992. He challenged this decision in court, and was re-instated." I couldn't find the detailed study report, but it appears to have been the usual toxic stimulus in isolation study typical of the many I have seen in studies of contributing factors' adverse effects.

The cover-up referred to re-stating the results of a study performed by an NTP contractor. The internal memo Marcus wrote describing an NTP contractor review meeting showing that ***every one of the cancers reported by the contractor had been downgraded by the NTP*** can be found here

(http://www.toxicteeth.org/health/cancer/ntp/marcus-memo.html).

A 1995 interview with Dr. Marcus describing his experience can be found here:

(http://fluoridealert.org/content/marcus-interview/). At this interview, Dr.

Marcus described the NTP actions at the review meeting thusly: "Now I've been in the toxicology business looking at studies of this nature for nearly 25 years and I've never seen that; never ever seen where ***every single endpoint that was a cancer endpoint had been down-graded***.....I found that very suspicious and I went to see an investigator in the Congress at the suggestion of my friend Bob Carton. And this gentleman and his staff investigated very thoroughly and found out that ***the scientists at the NTP down at Research Triangle Park had been coerced to change their findings.***"

In Senate testimony that included comments on the NTP final report on the contractor study,

(http://www.actionpa.org/fluoride/hirzy.html)

Dr. William Hirzy stated: "In 1990, the results of the National Toxicology Program cancer bioassay on sodium fluoride were published (10), the initial findings of which would have ended fluoridation. But a special commission was hastily convened to review the findings, resulting in the salvation of fluoridation through systematic down-grading of the evidence of carcinogenicity. The final, published version of the NTP report says that there is, "***equivocal evidence*** of carcinogenicity in male rats," changed from "***clear evidence*** of carcinogenicity in male rats." " Where have we heard that before? ***Plus ça change, plus c'est la même chose!!***

There is no reason to believe that EPA is the only government organization that would manipulate results to achieve a predetermined agenda, or fluorine is the only toxic stimulus for which this was done. In my JDIS paper, I listed similar distortions of results by other regulatory agencies, and could have listed many more examples had I had the space!