EFFECTS OF TOXIC STIMULI COMBINATIONS ON DETERMINATION OF EXPOSURE LIMITS

by

Dr. Ronald N. Kostoff
Research Affiliate, School of Public Policy, Georgia Institute of Technology
Gainesville, VA, 20155

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ABSTRACT

This monograph addresses the effects of toxic stimuli combinations on determination of safe Exposure Limits. It shows these combinations 1) typically lower the threshold constituent exposure levels associated with damage compared to 2) tests of combination constituents run in isolation. The monograph concludes 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 fully protective against serious adverse health effects.

While radiofrequency radiation (RFR) is used for illustrative purposes in a number of the examples presented, the conclusions are applicable to essentially all potential contributing factors to disease amenable to Exposure Limits. RFR combinations are the focal point in Appendix 2, where their potential role in contributing to the national/global opioid epidemic is also discussed.

INTRODUCTION

Single Stressor Studies

Since the dawn of the Industrial Age, and especially over the past century, many thousands of technologies and their products have been introduced to our society. There has been continual concern about the safety of these products, as reflected in their potential adverse impacts on human health.

As a result, a number of regulatory agencies have been established for the purpose of ensuring these technology products are safe. The mechanisms used by these agencies to determine safety have been of two main types: laboratory experiments (mainly on animals) and epidemiology studies (mainly on humans).

By far, the dominant approach has been single stressor studies, mainly on animals: "Over the past 35 years, the vast majority of risk assessments conducted by EPA have concentrated narrowly on individual chemical agents, distinct sources or source categories, and single exposure pathways, environmental media, routes of exposure, and health endpoints" [1]; "Traditional chemical-specific risk assessment based on animal testing may be insufficient and the lack of toxicological studies on chemical mixtures remains a major regulatory challenge." [2]; "The current chemical risk assessment approach is typically based on the toxicity caused by a single chemical on a variety of organs without acknowledging additional exposures to other chemicals also affecting the same organ or system." [3].

Multiple Stressor Studies

However, many biomedical studies have shown that combinations of stressors can enhance the adverse effects of any one of their constituents acting in isolation, with only a relatively few combinations decreasing the adverse effects of any constituent acting in isolation. Additionally, combinations of stimuli have conceptually similar effects on 1) treatments for diseases and 2) contributing factors to diseases. For treatments, usually, stimuli combinations 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. For contributing factors, usually, stimuli combinations allow less of each component to cause damage compared to the levels obtained when examining the effectiveness of each component in isolation (single stressor experiment, for assessing damage of the stimulus).

Thus, when setting safety/Exposure Limits for contributing factors in particular, safety/Exposure Limits for a given combination 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 stimuli components.

**Types of Combination Effects**

These types of combination effects include:

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);

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);

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

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) [4].

**Examples of Combination Effects**

Appendix 1 shows some of these multi-stressor combinations, and the resultant enhancement of adverse effects. 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 Exposure Limits based on experiments in isolation (single stressor experiments) and based on the actual experiments in combination could be substantial.

Items 4 - 7 show modest damage from each component of the combination in isolation (in the parameter range selected), but the enhancement afforded by the combination increases the damage substantially.

Item 8 is the same type as items 4-7, but reflective of an interesting application.

Items 9 - 10 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 an enhanced effect resulting in increased 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 the interactions of the constituents?

Sunlight, a human health requirement, may not be the main culprit here, at least in many cases not involving overexposure or predisposition. The main culprit may be the combinations of other potentially toxic stimuli (to which we are exposed) that result in a strong photosynthesizing effect.
Item 11 addresses multi-component mixtures. The two takeaways are 1) the enhanced effects predominated at lower effect levels, and 2) the relevance of enhanced effects increased with the complexity of the mixture. So, the greater the number of components, the more important the enhancements, 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 typically found in laboratory experiments may provide insufficiently protective safety/Exposure Limits, compared to the effects of larger combinations characteristic of the real world.

The Bibliography section (B) on Combined Toxicity and Enhanced Adverse Effects presents a much larger sample of combinations of stressors and their resultant impacts. But, even this Bibliography is a small fraction of multiple stressor combinations in the biomedical literature.

I have published two documents focused wholly on effects of non-ionizing radiation combined with other items, including both positive and negative effects of the combination [4-5]. The other items included (but were not limited to) chemical and physical. For radiofrequency radiation (RFR) in particular, the effects of RFR combined with one other stressor in lab tests can result in damage at lower RFR exposures than RFR exposures shown to cause serious damage when measured in isolation. The effects of RFR combined with myriad other stressors, as reflected in epidemiology studies, can result in serious damage at RFR exposures orders of magnitude less than RFR exposures shown to cause serious damage when measured in isolation.

As a specific example, consider the case of cell towers. The epidemiological studies on cell towers and cell phones reflect the real-world multi-stressor combinations to which people are exposed, although many of the constituent contributing factors to the combinations remain unknown. For higher accuracy in these types of studies, the test subjects would have to be instrumented to measure (at a minimum) 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 [6-8]. And, most of the cell tower studies don't report measurements of actual indoor exposures, so the actual power fluxes experienced by the residents could be an order of magnitude less than the numbers above for many of the residents in the so-called danger zone within a few hundred meters of the cell tower. Contrast this with the recent large-scale studies conducted by the National Toxicology Program (NTP) [9] and Ramazzini Institute [10], where RFR was applied in 'isolation', in single stressor tests. These studies showed statistically significant increases in cancer starting in the millions of microwatts/square meter.

It should be emphasized the above numbers apply to cancer incidence. There is a wide spectrum of adverse health effects from RFR that surface at much lower power flux levels. The Bioinitiative Report [11] provides a good summary of these adverse health effects, and the associated power flux levels at which they emerge. A recent study [12] summarizes the types of damage from electromagnetic field exposures and the myriad biological mechanisms that might cause this damage. Since many of these experiments involved single stressors, the real-world emergence of these adverse health effects can be expected to occur at much lower power flux levels when RFR is experienced as part of multi-stressor combinations.
Inadequacy of Existing Stressor Studies for Setting Exposure Limits

The reason few combinations (relative to single stressors) 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:

\[
C(n,r) = \frac{n!}{(r!)(n-r)!}, \text{ where } [!] \text{ denotes the factorial function.}
\]

For large \( n \), and \( r \) small compared to \( n \), \( C(n,r) \approx \frac{n^r}{r!} \). For large \( n \), \( C \) becomes a large number. How large? Consider the following, using RFR as an example.

It would be useful to identify comprehensively those substances that could combine with RFR to produce enhanced 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' [13] 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. There were about 8,000 causes identified for the ~4,000 diseases. On the order of 800 substances that contributed to at least a threshold number of the ~4,000 diseases were identified, and were labeled pervasive causes because of their widespread impact. The total number of causes identified for all diseases (~8,000) might be a good starting point for identifying additional potential RFR combinations.

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 impact one or more of these inter-related systems. Many of the studies focus 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) their adverse effects may have been suppressed from publication by the sponsor or journal.

First, let's examine two sub-sets of the 8,000 potential causes. 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 comprehensively their potential damage enhancements in concert with RFR?

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 instead examine combinations starting at the other end of the combinatorial spectrum.

For potential damage enhancements of RFR combined with \textbf{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 (eight runs total). In the combination experiment, sixteen runs total would be required.
For potential damage enhancements of RFR and two other contributing factors (a three component combination), \( \sim 500,000 \) 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 damage enhancements of RFR and three other contributing factors (a four component combination), 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 experiments required to cover all 1000 possibilities is completely unrealistic.

2. 100 contributing factors as possible RFR partners

For potential damage enhancements of RFR combined with one other contributing factor, 100 experiments would be required to cover all 100 contributing factors. For potential damage enhancements of RFR and two other contributing factors (a three component combination), 4,950 experiments would be required. For potential damage enhancements of RFR and three other contributing factors (a four component combination), 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 damage enhancements of RFR and one other contributing factor, 10 experiments would be required to cover all 10 contributing factors. For potential damage enhancements of RFR and two other contributing factors (a three component combination), 45 experiments would be required. For potential damage enhancements of RFR and three other contributing factors (a four component combination), 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.

**DISCUSSION**

The role of combinations in setting exposure limits

Again, we use RFR as the example, for illustrative purposes only. The arguments apply to any potentially toxic stimulus for which Exposure Limits need to be set.

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 Exposure Limits. Additionally, Exposure 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 safety objective function should be to minimize damage from the combination of potential contributing factors, since what will cause most damage to real people in the real world are (usually) combinations of myriad contributing factors. This requires a quasi-global optimization (on a given combination) rather than a local optimization (on any single constituent). A true global optimization over ALL potential combinations of contributing factors would ensure maximal protection for the public.

In the ideal situation for optimization over each combination, we would set a target for the combination based on 'acceptable' damage limits (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. The discipline called Cumulative Risk Assessment (CRA), or Cumulative Effects Assessment (CEA), accounts for multiple stressors acting through multiple pathways. It is not clear from some of the CRA/CEA papers I've read exactly how they would address a situation of the scale enumerated in the previous section on combinatorics. Many/most of these studies address relatively few combinations, with some of the studies examining different stressors from the same general class. For readers interested in learning more about CRA/CEA, the Bibliometrics section (A) on Cumulative Risk Assessment provides a number of useful references.

**Alternative approaches to identify combination effects**

RFR is again used as an example for illustrative purposes.

Clearly, 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. If a true global optimization is not possible to determine RFR Exposure Limits, then some less-than-perfect approach will be required. So, what alternatives exist to generate useful results for RFR safety/Exposure Limit setting?

Consider RFR cell towers, since a critical issue facing us presently is the proposed massive expansion of the cell tower network to accommodate the new 5G mobile system. For the past three decades, we have in fact been participating in a massive experiment where a significant number of human beings are exposed to RFR (and are exposed to many other potential contributing factors to disease in parallel) 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 enabled by 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 they present (for those in close proximity to the cell towers), 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 [9] and Ramazinni [10] isolated RFR exposure studies), and cancer incidence starts to increase within about 400-500 meters of the antenna [6-8]. There tends to be a latency time of a few years before the cancers appear, as one would expect.
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 monograph [14].

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 combinations by default, although the details of many of these combination components would remain unknown.

Relation of Biomedical Literature Findings to Setting of Exposure Limits

The above sections contain the implicit assumption that the (combinatorics constrained) existing data in the biomedical literature relevant to setting of Exposure Limits is fully taken into account when setting Exposure Limits. They also contain the assumption that the existing data in the biomedical literature can be trusted for accuracy. Both these assumptions may not be valid, for some cases.

For example, the Bioinitiative Report [11] and the recent Pall study [12] present copious examples of myriad types of adverse health impacts from athermal (non-heating) non-ionizing radiation, ranging from moderate to life-threatening. Yet, these athermal impacts are ignored completely by the FCC guidelines. For RFR, the FCC Exposure Limits (based on heating of tissue) are approximately six orders of magnitude above those shown to cause adverse health effects from single and multi-stressor studies. For all practical purposes, the FCC guidelines are non-protective for athermal exposures!

Is the setting of RFR Exposure Limits a unique case, or does it happen far more frequently than the public realizes? Appendix 3 contains another example, that of water fluoridation. According to the statements of a senior EPA toxicologist (who was fired for his remarks, then later re-instated), data from a single stressor experiment showing many instances of cancer associated with water fluoridation was downgraded by the government program manager for the research.

Reference [15], from which some of the data for Appendix 3 were taken, provides other examples of data manipulation that could impact setting of Exposure Limits. There is little reason to believe that the above examples of discrepancies between 1) results from single and multi-stressor experiments already conducted and 2) Exposure Limits set eventually are rare, especially for substances that are commercially or militarily sensitive.

In summary:

- Combinations of stressors usually lower the levels of each constituent associated with damage compared to levels of that constituent tested in isolation
- Exposure to combinations of stressors reflects the real-world
- Comprehensive testing of these combinations is severely limited by combinatorial considerations
- The results from some of these (mainly) single stressor and multi-stressor experiments that have been conducted may be manipulated and/or ignored for the purposes of setting Exposure Limits
CONCLUSIONS

Combining potential disease contributing factors typically reduces the threshold levels required to cause adverse effects from a particular exposure for any of the component contributing factors associated with the disease. Studies including these combinations are necessary to set credible safe Exposure Limits.

This monograph has presented two approaches for obtaining required combination data: lab animal (typically rodent) experiments with 'tight' controls on the contributing factor exposures, and epidemiological studies on health effects associated with exposures to contributing factors. The former approach has limitations based on species differences between test animals and humans, and sheer numbers of experiments required to approach the combinations reflective of the real-world. The latter approach has limitations based on not knowing the full 'signature' of each individual's exposure to potential disease contributing factors.

Despite their limitations, both approaches are useful. The former approach can provide relative impacts of adding contributing factors and observing the decrease in a given contributing factor threshold dose required to initiate serious diseases. It can 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 shown in the Introduction, most of these experiments used to determine Exposure Limits involve one 'stressor' in isolation (single stressor experiments). It is also my impression, from having read many thousands of combination effects papers across many substances and diseases, that combination enhancement 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 1) Exposure Limits that strongly depend on single stressor results and 2) Exposure Limits that would result from comprehensive potentially toxic stimuli combination studies until these combination studies have been conducted and their combination effects 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 fully protective against serious adverse health effects. Some Exposure Limits may be relatively more protective than others due to 1) results from lab and epidemiological studies being considered objectively, 2) safety factors being incorporated in decision-making, and 3) studies beyond single stressor being incorporated in the final determination. None have the full evidentiary base to inspire high levels of confidence in protection. Some Exposure Limits, such as those on RFR, offer essentially no protection for athermal exposures, based on what has been demonstrated and reported in the biomedical literature.

We will never be able to obtain a true global optimization over all potential combinations of potentially toxic stimuli to minimize adverse combination enhancement 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.
REFERENCES


[9] Toxicology and carcinogenesis studies in Hsd:sprague dawley SD rats exposed to whole-body radio frequency radiation at a frequency (900 MHz) and modulations (GSM and CDMA) used by cell phones; NTP TR 595; National Toxicology Program, National Institutes of Health, Public Health Service, U.S. Department of Health and Human Services. March 2018.


APPENDICES

Appendix 1 - Examples of non-RFR stimuli combination effects 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-heroain combination in PC12 cells"

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

8. "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.)
9. "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.)

10. "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”.)

11. "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 - Examples of RFR stimuli combination effects in biomedicine

The following four items are examples of combination effects that include RFR as one constituent of the combination:

1. "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.)

2. "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)

3. "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 ethynitrosourea (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).

4. "Suppressive effect of electromagnetic field on analgesic activity of tramadol in rats"
   (High frequency electromagnetic fields of 1500 and 1800 MHz when applied alone, did not influence pain perception threshold to thermal stimulus, however it presented an unwanted effect diminishing analgesic action of tramadol.)

Items 1 - 3 are additive or synergistic combinations that include RFR. All the example combinations shown consist of two stimuli. This is typical of lab experiments reported in the literature. Combinations of more than two stimuli in lab experiments are relatively rare, because of the combinatorics shown in the Analysis section.

Item 4 reflects antagonism at work in the combination. Combining EMF (at frequencies characteristic of cell phones/cell towers) with Tramadol reduced Tramadol's analgesic effect. In general, when calcium ion flow into neuronal cells is reduced, analgesic effects can be increased. In some regions of parameter space, exposure to EMF can activate the voltage-gated calcium channels, and could increase the flow of calcium into the neuronal cells [12]. Thus, in some cases, the effects of the EMF could antagonize the effects of the analgesic.

The effects shown in item 4 would need to be validated further for other RFR frequencies and other analgesics. If they are validated in much more extensive experiments, this could have major ramifications for the present-day nationwide opioid 'epidemic', as described in the following.

Potential contribution of RFR to opioid epidemic

The opioid 'epidemic' has been receiving much attention recently from myriad organizations, including the Administration and Congress. Given that this 'epidemic' is national/global, its causative factors must be operating at a national/global level.

Why are we having this 'epidemic'? Are more people getting injured, who require such pain-killers? Doubtful, given the myriad safety measures we have introduced into our workplaces and environment. Are surgeries becoming more painful? Doubtful, given the trend of reduced surgical invasiveness. What, then, would account for this 'epidemic'?
For simplicity, assume opioid addiction has two major categories of cause: non-pain-related and pain-related. The non-pain-related component tends to focus on individual-centric problems, such as peer pressure, impulsiveness, short-term outlook, potential genetic predisposition to addictive behavior, etc. The pain-related component encompasses physical and other types of pain.

It's difficult to see why there would be such a rapid increase in the non-pain-related causes of opioid addiction in recent years. These opioids have been readily accessible for a long time; why would the above individual-centric problems suddenly cause dramatic increases in their use? These individual-centric problems are certainly important and deserve attention, but we also need to look further.

It is far less difficult to explain the increase in the pain-related causes of opioid addiction (over and above the over-prescribing of opioids for pain resulting from myriad medical conditions), even though many stakeholder groups prefer to keep the main focus on the individual-centric problems.

Reference [13] shows there are many hundreds of 'pervasive' contributing factors that impact more than a threshold number of diseases. Most of the 4,000 diseases examined in [13] are chronic; their major symptoms take a long time to emerge. During the latency period, however, adverse impacts increase in the major networks of the body: the immune system, the neural system, the endocrine system, the circulatory system, etc. Given the strong inter-relationships among these networks, any adverse impacts on one network will have a ripple effect on the other networks. These adverse impacts would translate into symptoms, causing physical, mental, psychological, emotional, etc, discomfort. Taking more and stronger opioids is one approach to alleviate these increasing discomforts.

Many of these pervasive contributing factors result from the modern technology that has entered our workplaces and environment in recent years, relatively unregulated. Since the mid-90s, we have seen an explosion of wireless technology (cell phones, cell towers, WiFi, etc), increases in the use of pesticides such as glyphosate, increases in the number of vaccines on the recommended schedule, and myriad other technologies mentioned in [13]. Accompanying this rapid increase in inadequately tested and regulated technologies has been a parallel increase in harmful behaviors resulting from the technology introduction. Prolonged sitting at computers (prolonged sitting shown to be a pervasive cause of many diseases) is only one of many possible examples.

What we may have beyond the non-pain component is an increased opioid response to myriad pain-producing epidemics of our own making. We have a wireless radiation epidemic; we have an untested vaccine epidemic; we have a pesticide overuse epidemic! We have an epidemic of effectively untested and unregulated technologies flooding into the commercial, military, and personal sectors, and driving the increases in non-communicable diseases. These epidemics in combination cause increased discomfort, pain, and symptoms. We respond by increasing our use of opioids! Rather than face the existence of these pain-causing epidemics, we focus on the opioid response pain-killing epidemic.

Items 1 - 4 show that combinations of stimuli including RFR can both 1) increase symptoms and pain, and 2) reduce analgesic effects (the latter effect also being another variant on increasing pain). And, these four examples only involve combinations of RFR and one other stimulus. What happens in the case of real-world myriad stimuli in combination? Why wouldn't some of them exacerbate the pain-increasing effects of RFR and the analgesia decreasing effects of RFR? We can easily imagine a self-reinforcing situation with a large stimuli combination where 1) some members of the combination act in concert with the RFR to increase adverse symptoms and pain, and 2) other members of the combination act in concert with the RFR to decrease the analgesic effects of opioids given to reduce the pain. This would motivate the individual affected to increase the use of opioids to combat both the pain increase and the analgesia decrease from the combination above. This sequence increases the likelihood of opioid overdose!
Appendix 3 - EPA/NTP study on health effects of water fluoridation

This appendix summarizes a single stressor study used as one component in the determination of the safety of fluoridation. It derives from my JDIS paper [15], where 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 [16], and was fired in 1992. He challenged this decision in court, and was re-instated."

The cover-up (above) referred to re-stating the results of a study performed by an NTP contractor. Marcus wrote an internal memo describing an NTP contractor review meeting, where every one of the cancers reported by the contractor had been downgraded by the NTP [17].

At his 1995 interview [16], 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 downgraded.....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 [18], Dr. William Hirzy stated: "In 1990, the results of the National Toxicology Program cancer bioassay on sodium fluoride were published, 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."

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 [15], I listed similar distortions of results by other regulatory agencies, and could have listed many more examples had I had the space!
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AUTHOR BIO

Received a Ph. D. in Aerospace and Mechanical Sciences from Princeton University in 1967, and subsequently worked for Bell Laboratories, Department of Energy, Office of Naval Research, and MITRE Corp. Published over 200 peer-reviewed articles, served as Guest Editor of four journal Special Issues since 1994, obtained two text mining system patents, and presently is a Research Affiliate at Georgia Institute of Technology.

Published on numerous medical topics in the peer-reviewed literature, including:

- potential treatments for Multiple Sclerosis, Parkinson's Disease, Raynaud's Phenomenon, Cataracts, SARS, Vitreous Restoration, and Chronic Kidney Disease;
- potential causes of Chronic Kidney Disease and Alzheimer's Disease;
- potential treatment protocol for prevention and reversal of Alzheimer's Disease; and
- potential impacts of Electromagnetic Fields on health.

Listed in:
- Who's Who in America, 60th Edition (2006);
- Who's Who in Science and Engineering, 9th Edition (2006), and