Expert Review

Under-reporting of Adverse Events in the Biomedical Literature

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Abstract

Purpose: To address the under-reporting of research results, with emphasis on the under-reporting/distorted reporting of adverse events in the biomedical research literature.

Design/methodology/approach: A four-step approach is used: (1) To identify the characteristics of literature that make it adequate to support policy; (2) to show how each of these characteristics becomes degraded to make inadequate literature; (3) to identify incentives to prevent inadequate literature; and (4) to show policy implications of inadequate literature.

Findings: This review has provided reasons for, and examples of, adverse health effects of myriad substances (1) being under-reported in the premiere biomedical literature, or (2) entering this literature in distorted form. Since there is no way to gauge the extent of this under/distorted-reporting, the quality and credibility of the 'premiere' biomedical literature is unknown. Therefore, any types of meta-analyses or scientometric analyses of this literature

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will have unknown quality and credibility. The most sophisticated scientometric analysis cannot compensate for a highly flawed database.

Research limitations: The main limitation is in identifying examples of under-reporting. There are many incentives for under-reporting and few dis-incentives.

Practical implications: Almost all research publications, addressing causes of disease, treatments for disease, diagnoses for disease, scientometrics of disease and health issues, and other aspects of healthcare, build upon previous healthcare-related research published. Many researchers will not have laboratories or other capabilities to replicate or validate the published research, and depend almost completely on the integrity of this literature. If the literature is distorted, then future research can be misguided, and health policy recommendations can be ineffective or worse.

Originality/value: This review has examined a much wider range of technical and non-technical causes for under-reporting of adverse events in the biomedical literature than previous studies.

Keywords Under-reporting; Publication bias; Reporting bias; Manufactured research; Research misconduct; Research malfeasance; Biomedical literature

1 Introduction

Over the past century, the nature of research sponsorship in the USA has undergone significant transformations. Early sponsorship was by industry (mainly local), personal and organizational philanthropy, and universities themselves. World War II sponsorship was initially by the National Defense Research Committee, and then superseded by the Office of Scientific Research and Development. Today, we see mainly multi-Federal agency sponsorship, supplemented by typically corporate applied research and foundation research.

Government, industrial, and foundation sponsors have both missions and agendas. Sometimes, in order to further specific agendas, the integrity of the research product may have to be compromised. For example, critical research may go un-funded (Frickel et al., 2010), research findings may be suppressed (Martin, 1999a), and research may be 'manufactured' (Gotzsche, 2013; Kassirer, 2005). Some of the incentives for suppressing dissent in research are summarized by Delborne (2016), Martin (1999b), and Schumm (2015), and some specific examples of suppression of dissent in science include the research of Hess (1999), Kuehn (2004), Martin (2015), and McCulloch and Tweedale (2007).

Some of the reasons that industrial research tends to favor industrial products are shown in Amiri et al. (2014) and Krimsky (2003). Collusion among government, industry, and research performer organizations has been reported extensively, and valuable summaries can be found in Dickson (1984), Lewis (2014), and Primack and von Hippel (1974).

Why is this literature distortion important, especially in biomedical research? Almost all research publications addressing causes of disease, treatments for disease, diagnoses for disease, scientometrics of disease and health issues, and other aspects of healthcare build upon previous healthcare-related research published. Many researchers will not have laboratories or other capabilities to replicate or validate the published research, and depend almost completely on the integrity of this literature. If the literature is distorted, then future research can be misguided, and health policy recommendations can be ineffective or worse.

The remainder of the present paper will address issues related to the compromise of research integrity and under-reporting of adverse research results, with emphasis on the under-reporting of adverse events in the biomedical research literature.

2 Background

A 2015 eBook identifying pervasive foundational (tangible) causes of disease (Kostoff, 2015) implied that many adverse health events were not being reported properly in the literature. They had either not entered the published literature or had entered in a distorted form. The *technical* reasons for adverse health events not being reported fully in the literature are outlined in detail in Section 9A of Kostoff (2015). The reasons can be summarized as follows: if a potential foundational 'cause' for a disease (a foundational cause is a fundamental tangible cause that, in theory, is under human control, such as smoking, drinking, poor diet, excess exposure to radiation, overexposure to harmful chemicals, etc.) has not been researched, or its relevant data have not been entered into a tracking database, or has not been published in the appropriate venue, it will not show up in scientometric-type studies as a foundational 'cause'.

There is a vast body of literature describing the under-reporting of adverse events, e.g. Refs. [71–125] of Kostoff (2015) and the references in the Introduction of the present paper. The under-reporting means that some foundational causes will not appear at all in the literature, and other foundational causes will be linked to only a sub-set of the actual number of diseases impacted. The remainder of this paper emphasizes the *non-technical* reasons for under-reporting of adverse events.

3 Findings

3.1 Incentives and Policy Implications for Under-reporting of Adverse Events

This Section provides more details about under-reporting of adverse events. The analytic approach to be presented consists of four sequential steps:

- To identify the characteristics of literature adequate to support policy;
- To show how each of these characteristics gets degraded to inadequate literature;
- To identify incentives for inadequate literature; and
- To show policy implications of inadequate literature.

3.1.1 Characteristics of Adequate Literature

Characteristics of *adequate* literature for policy purposes include:

- All critical research problems necessary for credible policy are addressed/ funded;
- All research performed is credible and of high quality;
- All research findings are submitted for publication;
- All papers are reviewed by unbiased experts before publication;
- All high quality research submissions are published;
- All published articles are available to the general public; and
- All accessible articles are easily retrieved.

Each of the above characteristics will now be examined, and those factors that degrade each characteristic to one representing inadequate literature will be enunciated.

(i) Critical Research not Funded

Some critical research problems are not addressed/funded for myriad reasons (e.g. Frickel et al., 2010):

- The funds available to the sponsor organization are insufficient to cover all critical research areas;
- The process for setting funding priorities within the sponsor organization is poor; and
- External pressures effectively limit what topics can be funded, including (1) industry pressure to suppress topics that may have commercial sensitivity, and/ or (2) government pressure to suppress topics that may have political sensitivity. The pressures may operate intra-organizationally or inter-organizationally.

(ii) Research not Submitted for Publication

Some research findings are not submitted for publication for myriad reasons:

- National security classification, or classification for other reasons;
- Organizationally proprietary;
- No organizational or individual publishing tradition, with equally little motivation to publish; and

- Costs associated with submissions for publication (time and money), which some organizations may not be willing to spend.

Most disturbing is the potentially deliberate suppression of research findings (Anonymous, 2012). This may result from:

- Negative findings, which many organizations/journals/researchers are reluctant to publish;
- Adverse events, which many industrial organizations in the biomedical community and, as will be shown, even some governmental organizations in the biomedical community, are reluctant to publish;
- Commercial sensitivity, which industry would rather not be published;
- Political sensitivity, which government would rather not be published; and
- Unethical research, whose performers would rather not have it be published, and whose quality may be relatively low due to lack of research oversight and lack of reproducibility.

(iii) Poor Research Published; Good Research not Published

Some research that enters the literature may be of low quality, due to

- Poor peer review (where the peer review process and/or the peer reviewers are of low quality) or no peer review; and
- Contribution to the journal editor's pre-determined agenda.

Some high quality research may not get published, due to

- Poor peer review or biased peer review;
- Non-contribution to the journal editor's pre-determined agenda; and
- Not viewed as potentially contributing to increasing journal's impact factor.

(iv) Manufactured Research

Finally, some/much research that enters the published literature may be deliberately distorted or skewed; and can be called 'manufactured research' (Michaels, 2008; Oreskes & Conway, 2011). The purpose of this manufactured research is to both

- counter publications showing adverse effects from specific products, and
- sow confusion among the public and decision-makers, not allowing the consensus required for policy.

The book *Merchants of Doubt* describes this 'research manufacturing' process quite well (Oreskes & Conway, 2011). A few illustrative examples of some of the more egregious misrepresentations of science mentioned above, especially suppressed and manufactured research, will be presented in Section 3.2.

(v) Published Research not Easily Accessible

Some good published research may not be easily accessible to the public and the decision-makers, because of (1) publication in relatively obscure media; (2) publication behind high paywalls; and (3) poor search engines/algorithms.

(vi) Incentives for Inadequate Literature

There are many incentives for inadequate literature (e.g. Martin, 1999a), including

- Industry, which benefits from concealing the adverse effects of their products and services.
- Government, which supports corporate and large donor interests (through selective topic sponsorship and suppressed/distorted research findings) to lay the groundwork for future industry employment.
- Journal editors, who maintain industry-sponsored professional society and/or advertiser support through selective publication favorable to sponsors.
- Research performers, who receive and maintain grants by working on topics of interest to, and producing results desired by, corporate and government sponsors; produce publications aligned with the interests of journal sponsors or advertisers in order to increase publication likelihood; lay the groundwork for future industry employment and/or consultancies by not publishing findings antithetical to the interests of industry.

The above incentives (for inadequate literature) are grouped into four classes: industry, government, journal editors, and research performers. However, there are individuals who span multiple classes. For example, a person who works in government may also be a research performer and a journal editor. The incentive (for inadequate literature) associated with e.g. their government function may 'spill over' to their journal editor and research performer roles. So, even though the journal may not have industry or government financial support as a source of potential bias, the potential biases arising from the government or research performer affiliations of the editor could (in theory) influence the journal editor role.

(vii) Policy Implications of Inadequate Literature

There are myriad important drivers of government policy; the three critical drivers of policy considered now will be technical literature, interests of political donors, and interests of the electorate.

Three configurations that relate policy to technical literature will now be examined briefly.

First, the topical area is non-sensitive commercially or politically (e.g. weather satellite research, and age of universe research). There is little incentive for much 'manufactured research' in these topical areas. Donors and voters would agree with, or be indifferent to, policy dictated by adequate literature; donors and voters agree with policy dictated by inadequate literature; and policy reflects literature.

Second, the topical area is sensitive commercially and/or politically, e.g. climate change amelioration and EMF health impacts (Kostoff & Lau, 2013). There is incentive for much 'manufactured research' in these topical areas, and especially in the medical research area (Angell, 2005). In this case, donors and voters would *disagree* with policy dictated by adequate literature. The donors are driven by profit, and the voters are addicted to the specific technology (e.g. fossil fuels, and wireless communications) in this case. Thus, donors and voters agree with policy dictated by inadequate literature.

In the case of EMF health impacts, the policy on EMF exposures that would be required as the result of objective reading of the credible technical literature (severe restrictions on the use of wireless communications, etc.) would not be acceptable to the vast majority of donors and voters. In the case of climate change amelioration, the policy on CO_2 emissions from fossil fuels that would be required as the result of objective reading of the credible technical literature (extremely severe restrictions on the use of fossil fuels for energy generation starting today, etc.) would not be acceptable to the vast majority of donors and voters. Thus, the policy in practice reflects the interests of the donors and voters, not the dictates of adequate technical literature.

Third, the topical area is sensitive commercially and/or politically (e.g. exposures/treatments that cause disease (Kostoff, 2015)). Again, there is incentive for much 'manufactured research' in this case. Here, donors would disagree with policy dictated by adequate literature, whereas the voters would *agree* with policy dictated by adequate literature. The donors are driven by profit, whereas the voters are driven by the benefits of technology in this specific case. Unlike the previous configuration, the voters are not addicted to the technology, since its application may be unpleasant in many cases.

The donors still agree with policy dictated by inadequate literature, whereas the voters agree with policy dictated by inadequate literature, *only because they believe it is adequate.* This means that some literatures may be highly manufactured to maintain voter support. The policy reflects donors, not adequate technical literature.

In conclusion, the published technical literature is inadequate for myriad reasons, and the degree of inadequacy is unknown and may be unknowable. The fraction of inadequacy due to deliberate misinformation is unknown, but may be large for topical areas with commercial or political sensitivity.

3.2 Illustrative Examples of Under-reporting of Adverse Events

The literature on under-reporting of adverse events is large, and there is a wide spectrum of specific examples that could be presented. Because of limited space in this paper, a few representative examples from four groups (industry, government, journals, and researchers) will be presented. All these examples are from the USA experience. While many areas of science could be addressed, the focus of this paper is adverse events from the biomedical literature.

The most difficult cases to identify revolve around what is being covered-up. It is hard to determine what research is not being funded because of deliberate 'intent', or what research is not submitted for publication because of 'intent'. Much information in these types of cases is revealed because of courageous 'whistle-blowers', or from 'discovery' in legal proceedings.

3.2.1 Industry

There are literally thousands of industrial products, processes, practices, and services that could be contributing factors to myriad diseases in isolation or in combination (Kostoff, 2015). It would be to the financial advantage of the responsible industries if the adverse effects resulting from these products, processes, practices, and services were concealed from the public and policymakers.

Myriad studies have been reported/published showing how the science has been distorted by skewed literature, skewed panels, and skewed media, etc., as shown in the references of the present article, and their references. But, this is the tip of the iceberg. Such evidence of skewing and distortion is extremely difficult to obtain. Miscreants take great pains to conceal such misconduct, and many exposures of such activities are eventually revealed only through whistle-blowing or lawsuits. Because whistle-blowing tends typically to result in professional and financial suicide (Interview, 1995; Lewis, 2014), only a very few are willing to risk the repercussions. Thus, most of the science distortions remain hidden from public view.

Further, because of potential media involvement in science distortion and concealment (as will be shown in some of the examples in the present Section), public disclosure of these misdeeds may not necessarily occur in the mainstream media outlets or the most prestigious science and technical journals. Some of the references in this paper are Web page URLs. While these types of references are discouraged in mainstream journal publications, unfortunately (in some of the more egregious examples), these websites are the only media sources sufficiently courageous to challenge the distorted (or expose the concealed) messages promulgated by government and industry.

Two examples of distorted science/literature from industry will be presented: tobacco smoking and asbestos. Much of the incriminating evidence in both cases resulted from 'discovery' (in the legal sense) from lawsuits. The literature in both these examples is vast, and only a few references will be presented.

(i) Tobacco Smoking

Distortion of science by the tobacco industry has probably had the most extensive reporting and analysis. Due to the 'discovery' required by the numerous lawsuits filed against the tobacco industry, there has resulted a treasure-trove of internal documents made available for people to analyze.

Lisa Bero has written/contributed to numerous documents on the distortion of science by the tobacco industry (Bero, 2005; Glantz et al., 1996). She concluded that "The industry's lawyers and executives have been involved in the design and conduct of industry-supported research as well as the suppression of research that has not been favorable to the industry." (Bero, 2005).

(ii) Asbestos

Inhalation of asbestos fibers can lead to inflammation and scarring of the lungs. This could increase the risk of lung cancer and mesothelioma, and possibly other cancers as well. Many lawsuits have been filed by potential victims for compensation.

Legal 'discovery' similar to that obtained in the tobacco lawsuits was obtained from lawsuits against asbestos manufacturers (LaDou, 2004). David Egilman concluded that "MetLife…further manipulated the results of scientific findings from major research institutions, delaying important knowledge about the asbestos-cancer relationship" (Egilman, Bird & Lee, 2013).

3.2.2 Government

Because of the close and 'revolving-door' relationships between many government agencies and industry, some of the incentives to distort and conceal science become applicable to government as well. Additionally, some technologies become critically important for government to conduct operations, and science can become distorted or concealed if the government places higher priority on continuance of these operations than on safety aspects.

In this Section, three USA Agency examples of potential government distortion of science are presented: Enviromental Protection Agency (EPA), Centers for Disease Control and Prevention (CDC), and Food and Drug Administration (FDA). Consistent with the biomedical focus of this paper, the three agencies selected are health-related.

(i) Enviromental Protection Agency (EPA)

A Biosludge

In 1993, EPA generated a sludge rule that allows very toxic biosolids, or treated sewage sludge, to be used for farms, forests, playgrounds, and parks, etc. (Federal Register, 1993). Dr. David Lewis (ex-EPA senior researcher) exposed how EPA, in coordination with other Federal Agencies, research institutions, and advisory groups, suppressed public knowledge of potential biosludge adverse health effects for years (Lewis, 2014).

He did this exposure through

- published research articles;
- testimony and depositions before Congress;
- testimony and depositions before Department of Labor hearings; and
- lawsuits that revealed (under oath) the detailed participation of EPA officials and others in the science distortions.

Dr. Lewis was forced to retire and, in 2014, published a book (recounting his experiences) entitled *Science for Sale* (Lewis, 2014). He

- implied that EPA-sponsored research had to support EPA policy;
- implied that there was selective funding of scientists who supported EPA's sludge rule;
- showed myriad ways the science was distorted to present biosludge as safe; and
- showed collusion among EPA and other agencies.

The book is unique in its portrayal of collusion among the diverse groups mentioned in its sub-title: "*How the US Government Uses Powerful Corporations and Leading Universities to Support Government Policies, Silence Top Scientists, Jeopardize Our Health, and Protect Corporate Profits*". The biosludge example presented here, the more extended example of the measles, mumps and rubella (MMR) vaccine in Section 3.2.2, and the example of EMF adverse effects from Carpenter and Sage (2012), provide strong evidence that what we have in practice (for these commercially and politically sensitive issues) is a *Government-Industrial-Media-Complex* that monopolizes the discourse and exerts strong influence on what the public knows and believes about these topics.

B Fluoridation

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.

There is vast literature on the benefits (Newbrun & Horowitz, 1999; Yeung, 2008) and risks (Colquhoun, 1997; Hirzy, 1999) of water fluoridation. A very credible comprehensive review concludes, in part: "Due to its insatiable appetite for calcium, fluorine and fluorides likely represent a form of chemistry that is incompatible with biological tissues and organ system functions. Based on an analysis of the effects of fluoride demonstrated consistently in the literature, safe levels have not been determined nor standardized. Mounting evidence presents conflicting value to its presence in biological settings and applications." (Prystupa, 2011).

Unfortunately, the literature remains infested with voluminous 'manufactured' research on the safety of fluoride, sowing confusion on appropriate limits of fluoride concentrations in water. The EPA maximum contaminant level goals (MCLG) limit of 4 milligrams per liter for fluoride remains in effect, even though the Public Health Service recommends 1/6 that concentration as a limit. A study using fractional polynomials to determine the safety of fluoride levels in water for China concluded: "the safety threshold of fluoride in drinking water of our country is determined as 0.8 mg/L." (Pan et al., 2014).

Interestingly, EPA's risk control methodology, the Reference Dose (daily dose that a person can receive over the long term with reasonable assurance of safety from adverse effects), when applied to neurotoxicity data, led to a Reference Dose for fluoride of 0.000007 mg/kg per day. Persons who drink about one quart of fluoridated water per day from the public drinking water supply of the District of Columbia while at work receive about 0.01mg/kg per day from that source alone. This amount of fluoride is more than 100 times the Reference Dose (Hirzy, 1999).

This level of discrepancy between doses yielding adverse health effects shown in the literature and regulatory agency guidelines is not unique to either fluoridation or the EPA. For example, in a major study of adverse health effects from electromagnetic fields (Carpenter & Sage, 2012), the *Bioinitiative Report* shows orders of magnitude differences between (1) demonstrated adverse health impacts from Electromagnetic Field (EMF) and (2) Federal Communications Commission (FCC) and regulatory advisory body guidelines.

(ii) Centers for Disease Control and Prevention (CDC)

A Background

This lengthy example addresses alleged CDC cover up of an in-house study that showed potential links between increased risk for autism and MMR vaccine timing. Extra space is devoted to this example because of the potential personal and financial

consequences of under-reporting the adverse effects. Before the specific allegations are presented, some background of past MMR vaccine-autism link studies is required for context.

The controversy over a potential link between autism/behavioral disorders and the MMR vaccine seems to have originated in a 1998 *Lancet* Article (Wakefield et al., 1998). The article concludes: "Onset of behavioural symptoms was associated, by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children…All 12 children had intestinal abnormalities…chronic inflammation in the colon in 11 children…Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two)."

1) Studies Showing no Link between MMR Vaccine and Autism

Since that time, substantial research has examined potential links between MMR vaccine and autism. A 2014 meta-analysis of five cohort studies and five case control studies published in the journal *Vaccine* concluded: "Findings of this meta-analysis suggest that vaccinations are not associated with the development of autism or autism spectrum disorder. Furthermore, the components of the vaccines (thimerosal or mercury) or multiple vaccines (MMR) are not associated with the development of autism or autism spectrum disorder (Taylor, Swerdfeger & Eslick, 2014)." A 2015 study of autism occurrence by MMR vaccine status among US children with older siblings with and without autism concluded: "In this large sample of privately insured children with older siblings, receipt of the MMR vaccine was not associated with increased risk of autism spectrum disorder (ASD), regardless of whether older siblings had ASD. These findings indicate no harmful association between MMR vaccine receipt and ASD even among children already at higher risk for ASD (Jain et al., 2015)." Conclusions from the two studies referenced above typify the conclusions from other large-scale studies in the open peer-reviewed literature on potential links between the MMR vaccine and autism.

2) Studies Showing Potential Links between MMR Vaccine and Autism

However, conclusions from smaller-scale studies are suggestive of a linkage between MMR vaccine and autism. One study concluded: "the MMR antibody in autistic sera detected measles HA protein, which is unique to the measles subunit of the vaccine. Furthermore, over 90% of MMR antibody-positive autistic sera were also positive for MBP autoantibodies, suggesting a strong association between MMR and Central Nervus System (CNS) autoimmunity in autism. Stemming from this evidence, we suggest that an inappropriate antibody response to MMR, specifically the measles component thereof, might be related to pathogenesis of

autism" (Singh et al., 2002). A second study concluded: "The higher the proportion of children receiving recommended vaccinations, the higher was the prevalence of AUT [autism] or SLI [speech language impairment]. A 1% increase in vaccination was associated with an additional 680 children having AUT or SLI" (DeLong, 2011). Finally, a third study concluded: "autoimmune response to dietary proteins and deficient immune response to measles, mumps and rubella vaccine antigens might be associated with autism, as a leading cause or a resulting event" (Kawashti et al., 2006).

3) Correlations and Potential Synergies

The MMR vaccine was licensed in 1971 (Vactruth, 2013). Single MMR vaccine dose appears to have been used until 1989 (Bloom et al., 2006, Figure 1; CTDB, 2014), at which point the second dose MMR recommendation was made and implemented. The graphs in the references above show the MMR vaccination rate to have been approximately constant over the next twenty years, although other vaccines have been added to the schedule.

Since the mid-1990s, the autism rate (in children age six) has risen by an order of magnitude (Scutti, 2015). As the figure in the reference shows, that rate mirrors quite well the increase in use of glyphosate. Of course, correlation does not necessarily equal causation, but, when supported by one or more mechanisms, it provides a compelling argument. Dr. Seneff provides a plausible mechanism(s).

Cell phone subscriptions have also risen dramatically since the mid-1990s, and, in a 2009 study, correlated quite well with the increase in autism (BA, 2009). A number of researchers have provided plausible mechanisms, one of the more compelling recent ones being Dr. Martin Pall (Pall, 2015). He also believes there could be synergy between EMFs and toxic chemical *stimuli*.

There may be other contributing factors that would have some degree of correlation with the rapid increase of autism we have seen over the last two decades. The point is, if MMR vaccine usage has been roughly constant for the last two decades, and if autism has been increasing dramatically over that period, it is hard to make the argument that MMR vaccine *alone* is responsible for the increase. On the other hand, given the vast anecdotal evidence from many parents of how their children regressed shortly after receiving MMR vaccination, it is clear that the MMR vaccine, and possibly some of the other vaccines that have been added to the recommended schedule, are contributing factors. The question is: how does the MMR vaccine (and other vaccines) contribute to the development of autism within the context of parallel increasing exposures to glyphosate, wireless radiation, and many other potential contributing factors? Is the MMR vaccine an enabler/promoter of autism?

Could the increased rates of autism have come about without the introduction of these vaccines, since these increased rates parallel the increase in these other non-vaccine toxic *stimuli*? Unfortunately, that is not the experiment we, as a society, decided to run; therefore, the potential synergies between the MMR (and other) vaccine and the other potentially toxic *stimuli* cannot be excluded.

4) CDC Senior Researcher Allegations

Most troubling, a series of allegations from an employee of the Federal agency responsible for monitoring vaccine safety (CDC) suggests there may be a potential link between the MMR vaccine and autism, and documentation of the link has been suppressed deliberately. On August 27, 2014, the following excerpted statement by Dr. William Thompson (a CDC Senior Researcher) appeared on the website of Morgan Verkamp, LLC, a legal organization representing Dr. Thompson (Morgan Verkamp, 2014).

> "*I regret that my coauthors and I omitted statistically significant information in our 2004 article published in the journal Pediatrics. The omitted data suggested that African American males who received the MMR vaccine before age 36 months were at increased risk for autism. Decisions were made regarding which findings to report after the data were collected, and I believe that the final study protocol was not followed…*
>
> *My concern has been the decision to omit relevant findings in a particular study for a particular subgroup for a particular vaccine. There have always been recognized risks for vaccination and I believe it is the responsibility of the CDC to properly convey the risks associated with receipt of those vaccines.*"

According to taped phone conversations between Dr. Brian Hooker and Dr. Thompson, not only were the African-American children who received the MMR vaccine at substantially greater risk for autism (as alleged by Dr. Thompson), but according to Dr. Hooker, Dr. Thompson mentioned that children of all races were shown to have an increased risk of '*Isolated Autism*' (young children, regardless of race, who had (1) received the MMR vaccine on schedule, as recommended by the CDC, and (2) had no other factors sometimes observed to accompany autism, such as cerebral palsy, mental retardation, and birth defects.)

The MMR vaccine-autism study to which Dr. Thompson referred had been performed shortly after the turn of the new millennium, and the stated results (no link between MMR vaccine and autism) had been published in the journal *Pediatrics* (DeStefano et al., 2004). As of September 1, 2016, the article has not been retracted by *Pediatrics*, despite the serious allegations of intentional omission of critical data by one of its co-authors.

Thus, according to Dr. Thompson's allegations of August 27, 2014, CDC had known for at least a decade that these two groups of children were at increased risk for autism from the MMR vaccine, and did not disclose this information to the public. Internal CDC memos also showed the *highest levels of CDC management* had been informed of these problems with the MMR vaccine since the early 21st century (NaturalNews, 2014).

According to Dr. Thompson's statement above, thousands of documents have been turned over to Congress. On July 29, 2015, the Congressman to whom Dr. Thompson provided the documents, Rep. William Posey (R-FL), made a five-minute speech on the Floor of the House (Posey, 2015), confirming and amplifying Dr. Thompson's revelations.

5) Relation of Published MMR Vaccine-autism Studies and Dr. Thompson's Allegations

The CDC study results, according to Dr. Thompson's allegations, appear to contradict those of the large-scale open literature studies. It could be that the sample in the CDC study (metro Atlanta) was an anomaly relative to the samples in the large-scale studies. It could be there were errors in the data analysis in the CDC study. Or, as in the cases reported in *Merchants of Doubt* (Oreskes and Conway, 2011), it could be the large-scale studies were performed with the specific objective of showing vaccines were safe, particularly the MMR vaccine.

Given that a senior credible researcher, Dr. William Thompson (CDC), was willing to risk his reputation, career, and finances by coming forward with his allegations, his statements cannot be dismissed easily. If his allegations can be confirmed, with the implication that the CDC *organization* had the objective of proving the MMR vaccine safe, then the credibility of *any* CDC in-house or sponsored vaccine study has to be questioned.

(iii) Food and Drug Administration (FDA)

A Clinical Trial Violations Unreported

Charles Seife is a journalism Professor at New York University. He performed a study whose objectives were "to identify published clinical trials in which an FDA inspection found significant evidence of objectionable conditions or practices, to describe violations, and to determine whether the violations are mentioned in the peer-reviewed literature." (Seife, 2015a). He examined "publicly available documents, dated from January 1, 1998, to September 30, 2013, describing FDA inspections of clinical trial sites in which significant evidence of objectionable conditions or practices was found." He found that "only 3 of the 78 publications (4%) that resulted

from trials in which the FDA found significant violations mentioned the objectionable conditions or practices found during the inspection. No corrections, retractions, expressions of concern, or other comments acknowledging the key issues identified by the inspection were subsequently published." He concluded that "when the FDA finds significant departures from good clinical practice, those findings are seldom reflected in the peer-reviewed literature, even when there is evidence of data fabrication or other forms of research misconduct." He provided additional perspective in a *Slate* magazine article (Seife, 2015b).

B FDA Safety Shortcuts

In an interview with *Truthout* magazine (Rosenberg, 2012), Dr. Ronald Kavanagh, a former drug reviewer for the FDA in the Center for Drug Evaluation and Research, describes some FDA safety shortcuts. His comments complement the findings of Dr. Seife above, and the two sets of comments reflect both good research not reaching the open literature and distorted findings being published.

C Accelerated Approval of Vioxx

In the 1980s/1990s, the FDA/Congress created programs to expedite approval of promising new drugs intended for unmet medical needs (Kesselheim et al., 2015). Since that time, numerous studies have been done to ascertain whether the shorter pre-approval review times are associated with increased risk of adverse events. The published results are mixed.

For example, a 2008 study (Olsen, 2008) concludes: "Results show that drugs receiving faster reviews are associated with increased counts of serious adverse drug reactions." Another 2008 study, supported in part by AstraZeneca Pharmaceuticals (Grabowski & Wang, 2008), concludes the opposite: "we find no association between the FDA's review time and adverse events."

The latter study used data from the FDA's Adverse Events Reporting System (AERS). The AERS is a passive surveillance system, and, as shown in (Kostoff, 2015), such voluntary tracking systems tend to grossly under-report adverse events. Further, the under-reporting problem becomes more severe with the passage of time and the inability to link the adverse event with the drug. In both of the above studies, and other published studies covering similar time frames, insufficient time has elapsed to allow determination of long-term adverse effects of the drugs on human beings.

Section 9D2 of Kostoff (2015) contains the example of Vioxx, a drug that was given accelerated approval by the FDA, and resulted in tens of thousands of premature deaths. The example shows the risks of decision-making without adequate data. These risks may be far more widespread in drug/vaccine approval than is

commonly realized, especially if potential long-term adverse impacts, and adverse effects across multi-generations, are included.

Most transgenerational studies of adverse substance effects tend to be focused on environmental causes (Nilsson et al., 2012; Nilsson & Skinner, 2014), but there are some examples of such studies for drugs (Kujjo et al., 2011; Zeh et al., 2012). The latter study on chemotherapy-induced late transgenerational effects is particularly troubling, both because of the scarcity of such studies in the literature and the transmission of adverse effects deep in the generational chain. Do we have a ticking time bomb from drugs that were prescribed decades ago whose transgenerational effects are important but were never studied?

3.2.3 Journals

(i) *Microwave News* (MN)

This Section will present one example of alleged journal bias on publishing adverse effects. As the reader will see, obtaining data to support and validate allegations of bias is extremely difficult in this case.

Dr. Louis Slesin has been publishing a newsletter addressing myriad issues related to microwave radiation, and it is aptly entitled '*Microwave News*' (MN). In 2006, MN published an article entitled *"Radiation Research" and The Cult of Negative Results* (Slesin, 2006). It was a unique study with major contributions from Dr. Henry Lai, a leading researcher in the technical area of the article. The study's focus was essentially to ascertain how reflective of the microwave-induced genotoxicity publications in the larger technical literature were those articles published in the journal *Radiation Research* on this topic. In short, MN found that:

- [In the larger technical literature on microwave-induced genotoxicity] "There is just about an even split between effect and no-effect papers";
- "A clear —and disconcerting— pattern emerges: 32 of the 35 studies that were paid for by the mobile phone industry and the U.S. Air Force show no effect. They make up more than 75% of all the negative studies. You don't need to be a statistician to infer that money, more often than not, secures the desired scientific result"; and
- "A similar loss of balance occurs when you look at only the papers published in *Radiation Research*…Over the last 16 years, only one positive paper on microwave genotoxicity has appeared in *Radiation Research*. During the same time, the journal has published 21 negative genotox papers. (Australia's Pam Sykes, the lead author of the lone positive paper, was denied money for a follow-up and soon moved on to other research areas.)…80% of the negative papers (17 out of 21) published in *Radiation Research* were paid for by either industry or the U.S. Air Force."

At this point, the statements in MN are only *allegations*. There could be journal bias, or the best papers submitted to the journal happen to be the ones showing the absence of an impact of microwaves on genotoxicity. How could this issue be resolved?

One could (in theory) re-evaluate the original peer reviews of all the manuscripts submitted to the journal on this topic for bias. Unfortunately, one would then have the issue of determining the biases of the second group of reviewers, a difficult task. Additionally, even for reviewers who are unbiased, there is not always complete agreement. Scientists can sometimes have very differing opinions on the value of the same concept. Proving deliberate bias for a journal is extremely difficult, and may border on the impossible in practice.

Finally, how well this particular example reflects all, or any, other technical/ biomedical journals, is unknown.

3.2.4 Researchers

In the past decade, a number of books have been published documenting the 'manufacturing' of scientific research and the attempted suppression of unfavorable research for the purpose of creating doubt about adverse effects of myriad substances. Two outstanding examples are *Merchants of Doubt* (Oreskes & Conway, 2011) and *Doubt is their Product* (Michaels, 2008). *Merchants of Doubt* examined myriad high-sensitivity technical issues, including smoking, climate change, acid rain, ozone hole, and DDT. It showed how disinformation was promoted using well-known scientists and front organizations. The disinformation was promulgated through think tanks, government panels, and all types of media including the research literature.

The biosludge example presented in Section 3.2.2. can be viewed as one example of how this disinformation is promulgated/disseminated. The purpose of this disinformation is to spread confusion and promote doubt, thereby delaying any policy for action due to the (manufactured) absence of a consensus.

4 Conclusions

This paper has provided reasons for, and examples of, adverse health effects of myriad substances (1) being under-reported in the premiere biomedical literature, or (2) entering this literature in a distorted form. Since there is no way to gauge the extent of this under/distorted-reporting, the quality and credibility of the 'premiere' biomedical literature is unknown. Therefore, any types of meta-analyses or scientometric analyses of this literature will have unknown quality and credibility. The most sophisticated scientometric analysis cannot compensate for a highly-flawed database.

Equally damaging is the effect of this flawed database on the larger scientific enterprise. Science can be viewed as a never-ending construction project, where the building blocks and support structures are the documents from past scientific studies. If some, or many, of these building blocks are flawed, the upper parts of the structure will be weakly supported, and may collapse. Through the citation process, the misleading findings at the lower parts of the structure are promulgated to the upper portions, and the dilution of quality increases. While the propensity for misconduct is greatest in areas of commercial and political sensitivity, the broad reach of basic science will have a 'spill-over' adverse impact on myriad directly and indirectly related areas of science.

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