September 19, 2016

Board of Supervisors
County of Santa Barbara
105 East Anapamu Street
Santa Barbara, CA 93101

Dear Board of Supervisors,

RE: REFUGIO AFTER ACTION REPORT – focus on human and animal health

I am writing with some concerns about missing elements or items that are insufficiently addressed in the After Action Plan you will be considering tomorrow, September 20.

As most of you know, I am a film-maker and was a member of the press corps during the entirety of the response to the Refugio/Plains oil spill from May 19, 2015 on. I am also on the Board of the Environmental Defense Center and have closely followed the work of EDC in connection with the spill. I have provided comments to federal interests looking for lessons from the spill.

First, I endorse all the comments in the letter you received from EDC.
Second, I want to address an issue that was not mentioned in the EDC letter and is not adequately addressed in the After Action Plan – namely, human health.

We are very fortunate that Santa Barbara County dodged a bullet in the Refugio Spill. We were fortunate that the hills of the Gaviota coast are sparsely populated. Had a spill of this magnitude occurred in a more populated area, the release of toxic materials in the air could have had much more serious and widespread effect.

The After Action report (p. 12) notes response by the County Public Health Department as a "primary strength" but then specifically calls for improvement in public health notifications (p. 13). I fully concur that public health notices were inadequate. They were not only not timely, but frankly, I don't believe I ever heard one. Responses to inquiries from the press were always reassuring but lacking any understanding or recognition that people (and their pets and livestock) were getting sick. The County made little or no attempt to use the press to get out the message that if people were feeling bad from fumes, getting headaches, having trouble breathing, vomiting, etc. they should see a doctor or health care provider who is trained to recognize, diagnose, and treat symptoms from oil-chemical exposure.

I have filmed a story of one ranch where both workers and owners got sick, dogs were throwing up, and no one was getting information that they needed to get to a doctor. When they did finally get to Urgent Care (the emergency room was

overcrowded), they were fortunate to find a doctor who, although not qualified to treat chemical pneumonia or chemical illness, was at least aware of occupational safety and environmental medicine (OSEM) and "google it" to learn how to diagnose and treat symptoms of exposure.

I talked with some of the young people who were on the beaches on May 19 "cleaning up the oil" – scooping it into orange buckets from Home Depot. You saw the footage on TV news (both local and national). Some of them were working in flip-flops, some with bare hands, some with gardening gloves. None of them were wearing adequate clothing to be in contact with the heavy sour crude oil that they were scooping up. When they were told it was dangerous, they kept on working because no one else was getting the oil off of the beaches at that time.

I urged some of those "volunteers" who chose to clean up the oil on May 19 to get blood tests and get checked out. Most didn't feel they needed to do that, because no county, state or federal authorities were warning or advising them of the short- and long-term health risks, to which they had exposed themselves. Some did report how sick they felt or that they had headaches. I have attached the latest literature review of these debilitating health impacts from exposure to oil spills. *This is very serious!*

We can expect, even anticipate, that ignorance regarding dangerous exposures and human health impacts will be the norm for hundreds of people who regularly swim, surf and recreate on the beaches and in the ocean. Even though we love our coastline and were horrified by the mess created by Plains, the reaction was either to get involved in "cleanup" or to continue using nearby beaches *because they knew nothing about the devastating and potential life-threatening or debilitating health risks of exposure for even a few hours.*

So, while the numbers of those who got exposed to toxic fumes and toxic materials voluntarily or involuntarily were relatively few, the number could be much higher if the next spill occurs in a more populated area.

There are useful recommendations about messaging on beaches in the After Action Report (p. 19).

We need the following:

1. Every doctor, nurse and health care provider in the County should be required to have current training to deal with health impacts of chemical illness and should be doing regular refreshers on this information.

This is especially critical now that the International Classification of Disease, ICD-10 is now in effect as of October 2015. ICD-10 recognizes chemical illnesses and is

necessary for insurance coding and reimbursement. There is no excuse not to have trained and qualified health care professionals ready to assist in future oil disasters. Our county contains a lot of industrial oil development - onshore and offshore. We have old pipelines and we have the ever-present risk of human error. No health professional should have to rely on "googling" it. (Thank heavens for all the info available online, but this does NOT substitute for Occupational Safety and Environmental Medicine training!). Our health care professionals should all be aware of the risks in our county and have updated training and periodic reviews.

2. **Every veterinarian in the County should also have training and information to care for the horses, cattle, cats, dogs and other pets exposed to toxic chemicals in the event of oil spills or gas leaks.**

This County is full of animal lovers and people with working animals as well as pets. I would think that they too would want to know that all creatures are cared for and cared about – not just our amazing wildlife. By the way, the Oiled Wildlife Care Network did an amazing job of using trained volunteers from all over the state to rehabilitate oiled birds (especially pelicans). OWCN is a model of how to prepare and use volunteers throughout the state to respond to emergencies. Of course hundreds of birds and mammals died in the spill without rescue or had to be euthanized. Unfortunately, once the oil gets inside of wildlife through breathing contaminated air, preening, or eating contaminated food, the oil debilitates them, too, and causes prolonged suffering and early death, as in humans.

3. **We need to have appropriate warnings of risks of chemical illness from contact with oil or exposure to oil fumes**.

These should be prepared in advance and be part of oil spill contingency plans. They should be issued to all media outlets immediately upon notice of an oil or other toxic spill, and they should be posted and visible in all our public buildings.

4. **Security personnel should be prepared to close beaches in the event of a spill and prevent people from exposing themselves to toxic risks they do not understand.**

Security personnel should also be trained to recognize symptoms of oil-chemical exposures and be authorized to advise people to seek health care providers trained in occupational safety and environmental medicine. They need the full 40-hour training with shorter annual refresher courses before a disaster, not the abbreviated 4-hour training after a disaster. The latter lacks much critical information.

And of course, if we have a much faster response to spills, land-based spills should never reach the ocean or beaches; but if they do, we should have well-trained and well-equipped professionals and volunteers available locally to do the job.

5. We need to have a fully trained volunteer corps IN THE COUNTY so that volunteers can hit the beaches immediately under the supervision of county personnel with full haz-mat gear.

[The Report at p. 37 discusses the high interest in volunteering and the need for improvement in training and use of volunteers.] I interviewed volunteers who got the abbreviated 4-hour training and were able to help in the clean-up. They responded favorably to their experience. They were glad to be able to be involved and feel that they could do something. A few thought they were not used in a meaningful way. As the Report notes (p. 37), "the quality of engagement was reported to be both positive and negative." From my vantage point, the use of volunteers in clean-up was too little, too late and looked a little silly: people in haz-mat suits with kitty litter scoops combed the beaches after the paid professional crews had cleaned most of the oil, while folks a bit down the beach played in the sand and swam in the surf.

See Recommendations 13.1 to 13.4. These are generally useful and important recommendations but fall short of calling for a sizable, continuously trained, stand by volunteer corps ready to do clean-up before workers are able to arrive from other counties or other states. *We know these local people will deploy first as first responders: we must protect our local residents from doing public service work that may result in debilitating chronic diseases that may follow even brief exposures to oil.*

Thank you for taking a close look at the After Action Report. I hope to see the contingency plans radically improved in the many ways suggested in the Report and in the comments you have received.

Appreciatively,

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Effects of exposure to oil spills on human health: Updated review

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ABSTRACT

Oil spills may involve health risks for people participating in the cleanup operations and coastal inhabitants, given the toxicological properties of the oil components. In spite of this, only after a few major oil spills (crude oil or fuel oil no. 6) have studies on effects of exposure to diverse aspects of human health been performed. Previously, Aguilera et al. (2010) examined all documents published to that date dealing with any type of human health outcome in populations exposed to oil spills. The aim of the present review was to compile all new information available and determine whether evidence reported supports the existence of an association between exposure and adverse human health risks. Studies were classified in three groups according to type of health outcome addressed: (i) effects on mental health, (ii) physical/physiological effects, and (iii) genotoxic, immunotoxic, and endocrine toxicity. New studies published on oil-spill-exposed populations—coastal residents in the vicinity of the spills or participants in cleanup operations—provide additional support to previous evidence on adverse health effects related to exposure regarding different parameters in all three categories considered. Some of the observed effects even indicated that several symptoms may persist for some years after exposure. Hence, (1) health protection in these individuals should be a matter of concern; and (2) health risk assessment needs to be carried out not only at the time of exposure but also for prolong periods following exposure, to enable early detection of any potential exposure-related harmful effects.

Advances in exploration and production activities have helped to locate and recover supplies of oil and natural gas from major reserves across the globe. At the same time, demand for petroleum-based products has grown in every corner of the world. Hence, these products need to be transported from their original oilfields to sites of demand. Since the first oil tanker began shipping oil in 1878 in the Caspian Sea, the capacity of the world's maritime tanker fleet has grown substantially. However, petroleum exploration and production operations, as well as its transportation by tankers or pipelines, entail risks of spill. The first large oil spill from an early supertanker was that from the *Torrey Canyon* on March 18, 1967, on the Isles of Scilly, Cornwall (United Kingdom), where 119,000 tons of oil were spilled. The explosion on the BP-operated *Deepwater Horizon* oil rig in the Gulf of Mexico on April 20, 2010, was the last and largest accidental oil spill in history (680,000 tons). International agreements, community regulations, and other different measures have been enacted in order to protect the marine and coastal environment, but ensuring strict compliance with these is difficult.

Crude oil is a complex combination of hydrocarbons consisting predominantly of paraffinic (straight and branched-chain alkanes), naphthenic (cycloalkanes or cycloparaffins), and aromatic hydrocarbons (American Petroleum Institute [API] 2011). Sulfur, oxygen, and nitrogen compounds, organometallic complexes, notably nickel and vanadium, and dissolved gases, such as hydrogen sulfide, are also found in crude oil. Similar hydrocarbons, heterocyclics, metals, and other constituents, such as hydrogen sulfide, are present in all crude oils but their proportions vary depending on the crude source (API 2011). Fuel oils are produced from crude petroleum by different refining processes depending on their intended use, and are composed of complex and variable mixtures of aliphatic (alkanes, alkenes, cycloalkanes) and aromatic hydrocarbons, containing low percentages of sulfur, nitrogen, and oxygen compounds (Laffon 2014). The precise chemical

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composition of each of the fuel oils may vary somewhat, depending upon the source, refinery involved, presence of additives or modifiers, and other factors (Laffon 2014). Crude oils are richer than heavy fuel oils in low-molecular-weight hydrocarbons (more volatile), but have lower proportions of sulphur- and nitrogen-containing compounds with high molecular masses and high boiling points. The toxicological profile of oils has been extensively detailed (API 2011).

Oil spills are among the most important ecological disasters, since they adversely affect aquatic and terrestrial ecosystems and produce significant economic losses. Further, oil spills may involve adverse health risks for people associated with cleanup operations and coastal inhabitants, given the toxicological properties of the oil components. In spite of this, there have only been studies on the effect of a few major oil spills (9 of 40), on psychological well-being and human health (Table 1). In six of these accidents (*Exxon Valdez, Braer, Sea Empress, Tasman Spirit*, and *Hebei Spirit* tankers, and *Deepwater Horizon* oil rig), the spill consisted of crude oil; in the three remaining cases (*Nakhodka, Erika*, and *Prestige*), the spill involved a heavy fuel oil (fuel oil no. 6, also named bunker C).

Previously, Aguilera et al. (2010) examined all documents available in the literature up to that date (2009) dealing with any type of adverse human health outcome in populations exposed to oil spills, including individuals working in the cleanup tasks or coastal residents in the vicinity of the spills. Subsequently, a series of additional studies was published on this topic regarding newly occurred accidental oil spills (*Hebei Spirit* tanker and *Deepwater Horizon* oil rig) or some former ones (*Prestige* and *Tasman Spirit* tankers). Therefore, the aims of the present review were to (1) compile all new information available regarding adverse human health effects following exposure to oil spills and (2) determine whether the evidence reported supports the existence of an association between exposure and adverse human health risks. Studies were classified into three groups according to the type of health outcomes assessed with (i) effects on mental health, (ii) physical/physiological effects, and (iii) genotoxic, immunotoxic, and endocrine toxicity.

Table 1. Oil spills from tankers or rigs for which human health effects have been assessed (chronologically ordered).

Accident	Spill size (t)	Type of spill	Place	Year
Deepwater Horizon	680,000	Crude oil	Gulf of Mexico, United States	2010
Hebei Spirit	10,900	Crude oil	Taean, Korea	2007
Tasman Spirit	37,000	Crude oil	Karachi, Pakistan	2003
Prestige	67,000	Fuel oil no. 6	Galicia, Spain	2002
Erika	20,000	Fuel oil no. 6	Brittany, France	1999
Nakhodka	>6,000	Fuel oil no. 6	Japan Sea, Japan	1997
Sea Empress	72,000	Crude oil	Milford Haven, UK	1996
MV Braer	85,000	Crude oil	Shetland islands, UK	1993
Exxon Valdez	37,000	Crude oil	Prince William, USA	1989

Mental Health Effects

Previously, Aguilera et al. (2010) demonstrated that most investigations conducted on human populations after oil spill accidents corresponded to cross-sectional epidemiological studies that assessed mental health consequences and/or acute physical effects in the exposed populations (cleanup workers or residents). Six years and two massive oil spills later the situation was not markedly different, although several new studies dealing with different clinical parameters and a number of follow-up studies were conducted.

Regarding specifically mental health effects, new studies published since 2009 were collected as presented in Table 2; the order follows the spills chronologically. The first studies carried out in oil spill exposed populations focused on psychological health after the *Exxon Valdez* accident, which occurred in 1989. Later, similar investigations were performed after the *Sea Empress* and *Prestige* spills (reviewed in Aguilera et al. 2010). General results showed higher scores or prevalence of depression, anxiety disorder, event-related psychological stress, and posttraumatic stress disorder in the oil-exposed populations. In addition, an important role for social/familial support and economic aid was reported as modulators of symptom manifestation where adequate social and economic support enabled the affected populations and communities to better cope with the distress of oil spills.

Table 2. Epidemiological studies on mental health effects related to exposure to oil spills published since 2009 (ordered by the chronology of the spills).

Accident and reference	Study characteristics	Methods	Results
Prestige—Sabucedo et al. (2010)	Cross-sectional, 1 year after the accident. Impact on mental health and perception of physical health and functional capacity in residents (N = 430).	SCL-36 scale for mental health symptoms, and 4 subscales from the SF-36 (General Health, Physical Role, Emotional Role, and Social Function) for physical health and functional capability.	Individuals with higher degrees of exposure or residing in areas closest to the spill show lower levels of mental health. Women and fishers tend to suffer more from the consequences of these types of disaster.
Prestige—Pérez-Pereira et al. (2012)	Cross-sectional. Effect on academic achievement and classroom behavior of preschool children (ages 5–6 years) (n = 106), school-aged children (ages 10–11 years) (n = 177), and adolescents (ages 15–16 years) (n = 147) living in 3 differently affected areas.	Academic qualifications in school records, CBI questionnaire reported by teachers, CSCY scale for coping strategies.	No general effect of the disaster on the preschool children. Primary school-aged children showed higher hostility to others after the *Prestige* than before. There was a higher effect on adolescents when compared to the other groups. Their academic scores were lower, and intelligent behavior, extraversion, and independence were higher, after the *Prestige* than before. In this group, academic achievement, but not schoolroom behavior, was influenced by coping strategies and family characteristics.
Hebei Spirit—Song et al. (2009)	Cross-sectional. Psychological health of the residents of Taean during the oil spill cleanup (N = 71). As comparison group, data from the existing studies that may represent a general Korean group were selected.	PWI scale for psychosocial distress, CES-D scale for depression, and a questionnaire on suicidal impulses.	When compared with unexposed groups in the general population, residents of Taean were 6.5 times as likely to have high stress and 9.4–9.7 times as likely to be depressed. No significant difference in the rate of suicidal impulse was found. Factors associated with high stress, depression, and suicidal impulses were age, a change in income, educational level, number of days working on the cleanup, and positive responses to questions about affected daily activity and hospital visit due to work on cleanup.
Hebei Spirit—Lee et al. (2010)	Cross-sectional. Acute health effects in residents from seashore villages of a heavily and moderately oil-soaked area and a lightly oil soaked area (10 villages from each area, 10 adults from each village, both genders).	Questionnaire on the characteristics of residents, the cleanup activities, the perception of oil hazard, depression (CES-D) and anxiety (STAI-X-1), and the physical symptoms.	The more highly contaminated the area, the more likely it was for residents to be engaged in cleanup activities and have a greater chance of exposure to oil. The indexes of anxiety and depression were higher in the heavily and moderately oil-soaked areas. Significantly increased risks of several physical symptoms, including headache, nausea, dizziness, whole body fatigue, sore throat, coughing, runny nose, skin flare, and sore eye were obtained.
Hebei Spirit—Ha et al. (2013)	Cross-sectional. Mental health in children (N = 1,362) living in the area affected by the spill.	Questionnaire with Korean versions of the Children's Depression Inventory and State Anxiety Inventory for Children.	Children with the closest distance (4th quartile) to the school from the contaminated coastline showed a significantly higher symptom risk for depression compared with those with the farthest distance (1st quartile). There was no significant association between anxiety symptoms and distance.

(*Continued*)

Table 2. (Continued).

Accident and reference	Study characteristics	Methods	Results
Hebei Spirit—Kim et al. (2013)	Cross-sectional, 1.5 years after the spill. BOD, including physical and mental diseases, of the residents living in contaminated coastal area (N = 10,171).	Questionnaires on exposure and medical problems, and to assess psychological health and asthma, and physical and laboratory examinations of respiratory, cardiovascular, neurological, and psychological systems	The YLD of mental diseases including PTSD and depression for men were higher than that for women. The YLD for women was higher in asthma and allergies (rhinitis, dermatitis, conjunctivitis) than that for men. The effects of asthma and allergies were the greatest for people in their 40s, with the burden of mental illness being the greatest for those in their 20s. Proximity to the spill site was associated with increased BOD.
Hebei Spirit—Choi et al. (2016)	Cross-sectional. Prevalence of psychological symptoms in residents of communities affected by the spill (N = 993).	Scales for PTSD (PDS), depression (CES-D), suicidal ideation (SSI) and anxiety (SCL-90-R).	The symptom prevalence of PTS, depression, suicidal ideation, and anxiety were 19.5%, 22.0%, 2.3%, and 4.2%, respectively, and symptoms were higher in people who were female, older, less educated, and had lower family income. Prevalence increased significantly along with increasing severity of oil exposure and was higher in people with a fishery or related occupation than in those with other livelihoods.
Deepwater Horizon—Abramson et al. (2010)	Cross-sectional. Psychological impact on coastal residents (children and families) (N = 1,203).	Telephone interviews on exposure, physical and mental health, and decisions related to oil spill on a daily basis.	More than one-third of parents reported that their children had experienced either physical symptoms or mental health distress as a consequence of the oil spill. One in five households has seen their income decrease as a result of the oil spill and 8% have lost jobs. More than 25% of coastal residents think they may have to move from the area because of the oil spill.
Deepwater Horizon—Grattan et al. (2011)	Cross-sectional. Acute levels of distress (depression, anxiety), mechanisms of adjustment (coping, resilience), and perceived risk in residents of fishing communities indirectly impacted (n = 71) or directly exposed (n = 23) to coastal oil.	Standard interview and formal neuropsychological, psychosocial, and risk perception measures (modified BOENQ and BMAST questionnaires, WHO Neurobehavioral Core Test Battery, POMS test, Brief COPE questionnaire, CD-RISC short form, HCEQ-V questionnaire).	No significant differences between community groups were found. Residents of both communities displayed clinically significant depression and anxiety. Relative to those with stable incomes, participants with spill-related income loss had significantly worse scores on anxiety, depression, fatigue, confusion, and total mood disturbance scales; had higher rates of depression; were less resilient; and were more likely to use behavioral disengagement as a coping strategy.
Deepwater Horizon—Osofsky, Palinkas, and Galloway (2011)	Cross-sectional. Effects on mental health of residents of areas affected by the spill (N = 452).	Telephone and face-to-face interviews assessing concerns and direct impact (also from Hurricane Katrina). Modified version of the Sheehan Disability Scale, CD-RISC, WHO-QoL, K6, and PCL-C scales.	The greatest effect on mental health was related to the extent of disruption to participant's lives, work, family, and social engagement, with increased symptoms of anxiety, depression, and posttraumatic stress.
Deepwater Horizon—Buttke et al. (2012a)	Cross-sectional, 4–5.5 months after the spill. Assessment of mental health effects in coastal residents (N = 469).	Questionnaire to evaluate physical symptoms, quality of life, mental health, social context and exposure	Negative mental health parameters were higher in the coastal communities than the state estimates and available estimates nationwide.

(*Continued*)

Table 2. (Continued).

Accident and reference	Study characteristics	Methods	Results
Deepwater Horizon—Buttke et al. (2012b)	Cross-sectional, 1 year after the spill. Follow up of Buttke et al. (2012a) study. Long-term mental health needs and changes in coastal residents (N = 596).	Questionnaire with standardized behavioral health questions on quality of life, depression, anxiety, and social context.	Higher proportion of negative quality-of-life indicators and social context outcomes were reported as compared to state reports, but these proportions were lower than those seen some months ago (Buttke et al. 2012a). Respondents reporting decreased income following the oil spill were more likely to show poor mental health symptoms.
Deepwater Horizon—Gill, Picou, and Ritchie (2012)	Cross-sectional. Mental health and social impacts in residents of south Mobile County (N = 412), and comparison with results obtained in Cordova (Alaska) residents, exposed to *Exxon Valdez* oil spill.	Telephone survey including a standardized measure of psychological stress (Impact of Event Scale), as well as measures of ties to resources, resource loss, perceptions of recreancy, risk perceptions, and demographic characteristics.	Event-related psychological stress among residents of south Mobile County. County was relatively high and similar to that of residents of Cordova. The strongest predictors of stress were family health concerns, commercial ties to renewable resources, and concern about economic future, economic loss, and exposure to the oil.
Deepwater Horizon—Lee and Blanchard (2012)	Cross-sectional. Community attachment and negative affective states in households from three coastal parishes (N = 935).	Telephone survey with demographic, health-related, and community attachment questions.	Higher level of community attachment was associated with significantly higher level of negative affect, after controlling for health-related measures that may have an impact on negative affect, such as stress or physical health. This finding holds for those tied to the fishing and seafood industry, to the oil industry, and those having no immediate links to either industry.
Deepwater Horizon—Werner and Locke (2012)	Cross-sectional. Mental health effects on 2 Gulf Coast communities 1 year after the spill, reported by mental health clinicians employed by Project Rebound (n = 17) and counselors from two school districts on the Gulf Coast (n = 4).	Interviews related to mental health response and recovery in the communities, to identify common stressors (family disruptions, job loss or change in economic conditions, financial pressures, and bureaucratic hassles) that emerge from the disaster.	One year post the oil spill, clinicians reported that families were still experiencing disruption. Due to the loss of economic opportunities and lifelong careers, families and communities reported increased financial pressures. Bureaucratic hassles in applying to Gulf Coast Claims Facility and receiving appropriate payment were also reported. The stress has reached a breaking point and individuals who have never needed to ask for help are now seeking services.
Deepwater Horizon—Locke and Werner (2013)	Cross-sectional. Delivery and utilization of mental health services, and role of stigma related to help seeking behavior, on 2 Gulf Coast communities 1 year after the spill (N = 17 mental health clinicians employed by Project Rebound and 4 counselors from two school districts on the Gulf Coast).	Interviews with questions for defining the disaster and recovery efforts, identification of people in need and service delivery, and challenges and needs for future disasters.	Clinicians experienced a number of stigma-related barriers to delivering services including self-stigma, public stigma, and cultural implications of seeking and receiving aid. Clinicians and school counselors found that the children were a vehicle to identify and provide services to families in need, which negated some of the initial stigma related to help-seeking behavior.
Deepwater Horizon—Morris et al. (2013)	Cross-sectional, 1 year after the oil spill. Persistence of mental health problems previously detected in communities from coastal regions (Grattan et al. 2011) (N = 93).	Background and history questionnaire as well as POMD, Impact of Event Scale, CD-RISC within the context of a broader psychological and neuropsychological examination.	A year after the spill, there was no significant change in levels of anxiety or depression in the cohort assessed. Income loss continued to be associated with higher levels of psychopathology; findings were not associated with age, gender, education, or psychiatric history.

(*Continued*)

Table 2. (Continued).

Accident and reference	Study characteristics	Methods	Results
Deepwater Horizon—Cherry et al. (2015)	Cross-sectional. Predictors of long-term psychological outcomes in current residents of disaster-affected communities (Hurricanes Katrina and Rita, and Gulf oil spill) (n = 63) and fishers (n = 64), former coastal residents (n = 62), and indirectly affected noncoastal resident controls (n = 30).	Measures of PTSD (PTSD Checklist-Civilian Version), depression (PHQ-9), anxiety (GAD-7), religiosity (RQ), perceived social support (Interpersonal Support Evaluation List), and storm exposure (SSQ).	Nonorganizational religiosity was a significant predictor of PTSD. More frequent participation in nonorganizational religious behaviors was associated with a heightened risk of PTSD. Low income and being a coastal fisher were significant predictors of depression symptoms. Perceived social support had a protective effect for all mental health outcomes.

Note. Studies assessing both mental and physical parameters are included in this table. BMAST, brief Michigan Alcohol Screening Test; BOD, burden of disease; BOENQ, Boston Occupational and Environmental Neurology Questionnaire; CBI, Classroom Behavior Inventory; CD-RISC, Connor-Davidson Resilience Scale; CSCY, Coping Scale for Children and Youth; CES-D, Center for Epidemiologic Studies–Depression; GAD, generalized anxiety disorder; HCEQ-V, Health and Coastal Environment Questionnaire-V; PDS, Posttraumatic Diagnostic Scale; POMS, Profile Of Mood States; PCL-C, Posttraumatic Symptom Checklist for Civilians; PHQ, Patient Health Questionnaire; PTSD, posttraumatic stress disorder; PWI, Psychological Well-Being Index; RQ, Religiosity Questionnaire; SCL-36, Symptom Checklist-36; SCL-90-R, Symptom Checklist-90-Revision; SF-36, Short Form-36; SSI: Scale for Suicidal Ideation; SSQ, Structured Storm Questionnaire; STAI-X-1, State-Trait Anxiety Inventory; WHO, World Health Organization; WHO-QoL, WHO quality of life; YLD, years lived with disability.

Prestige

A study carried out 1 year after the *Prestige* sinking evaluated the consequences of the oil spill on residents of affected coastal areas in terms of perception of mental health, physical state, and functional capacity for fulfilling different roles (Sabucedo et al. 2010). In addition, exposure was assessed by using four items from the Exposure Status Scale compiled by Palinkas et al. (1993) for the same purposes in the *Exxon Valdez* study. Individuals closer to the oil spill location presented a clinical pattern characterized by an increased frequency of psychopathological symptoms (such as somatization, anxiety, and hostility), and a lower perception of physical health and functional capacity. Analyses of different sociodemographic variables showed that fishers experienced the consequences of the spill more intensely. Moreover, a significant interaction between gender and exposure status with regard to somatization, general health, and emotional role was demonstrated, with women being perceived to be in worse conditions. This study confirmed the results of a former investigation in residents and controls 16 months following *Prestige* spill, reporting that coastal residents in the most affected area presented worse scores than controls for mental health dimension of the SF-36 questionnaire, and a higher frequency of suboptimal values in the Goldberg Anxiety and Depression Scale (GADS) (Carrasco et al. 2007). It is of interest that Sabucedo et al. (2009) previously demonstrated that the feelings of support from the community and satisfaction with financial aid received are crucial factors in alleviating the psychological impact on populations affected by such events, even 1 year after the accident.

Further, the influence of the *Prestige* oil spill on academic achievement and classroom behavior of children (preschoolers and school-aged) and adolescents residing in differently affected areas from the Galician coast were studied during the academic years previous to and after the spill (Pérez-Pereira et al. 2012). This study was carried out from an ecological perspective, that is, considering psychological development in the framework of the interactions between children and the context where children live. Data demonstrated relatively minimal consequences. No apparent general effects were observed in the preschool children. Primary school-aged children presented higher hostility to others after the spill than before, indicating problems of social adjustment. The adolescent group was the most affected when compared to other groups, and their academic scores were lower after the spill than before. Coping strategies and family characteristics had impact on the adolescents' academic achievement, but not on their schoolroom behavior.

Hebei Spirit

Four different investigations evaluated mental health consequences in different populations exposed to the *Hebei Spirit* spill. Psychosocial distress, depression, and suicidal impulses were assessed by Song et al. (2009) in a small group of residents of Taean County (South Korea). Higher risks of stress and depression, but not suicidal impulse, were observed in residents exposed to oil than in controls. Results of these indices were influenced by age, a change in income, educational level, duration of participation in the cleanup, and positive responses to questions about affected daily activity and hospital visits due to work on cleanup. Analysis of prevalence of psychological symptoms in a larger group of residents of coastal communities (approximately 1000) (Choi et al. 2016) indicated that symptoms of posttraumatic stress disorder, depression, suicidal thoughts, and anxiety were prevalent, and increased according to exposure level or proximity to the oil spill. This was attributed to a direct effect of the disaster itself, as well as a significant association with occupation (higher in subjects with a fishery or related occupation than in those with other livelihoods), which was described as an indirect influence or economic damage/income loss as a result of the disaster.

Similarly, when comparing residents from areas differently affected by the *Hebei Spirit* spill, exposure to oil (evaluated by means of questionnaires) and engagement in cleanup activities frequency of effects were higher in residents from heavy and moderately oil soaked areas than in residents from lightly oil soaked areas, as were the indices of anxiety and depression (Lee et al. 2010).

Depression and anxiety were also assessed by Ha et al. (2013), but specifically in children living in the *Hebei Spirit* spill-affected area. The investigators divided the child population in quartiles according to distance of school they attended from the contaminated coastline, and observed significantly higher symptom risk for depression, but not anxiety, in children with the closest distance (4th quartile) compared with those with the farthest distance (1st quartile).

Kim et al. (2013) were the first to quantify the burden of disease (BOD) due to an oil spill, in a large group of residents (greater than 1000). BOD is necessary to assess the scale of health damage at the population level as well as the associated compensation costs (Kim et al. 2013). Data demonstrated that BOD for 1 year for the residents living near contaminated coastal areas was significant and related to proximity to the spill, as well as to participation in cleanup efforts; posttraumatic stress disorder, together with asthma, was found to comprise the most prominent disease burden in the contaminated areas. On the basis of variations found in health impacts of oil spill related to age, gender, and region, a community-specific rehabilitation policy was recommended.

Deepwater Horizon

Most studies dealing with mental health effects published since 2009 analyzed the *Deepwater Horizon* spill-exposed populations, due to the extensive research efforts made to assess the consequences on human health after that accident, and the priorities established by the committee to review the federal response to the health effects associated with the Gulf of Mexico oil spill (behavioral health, exposure assessment, seafood safety, communication, and developing a research response framework for disasters) (Institute of Medicine [IOM] 2010).

Nevertheless, results from these studies need to be interpreted cautiously since Hurricane Katrina, described as the worst natural disaster in U.S. history, devastated the Gulf Coast (mainly Louisiana, Mississippi, and Alabama) on August 29, 2005. When the *Deepwater Horizon* explosion and oil spill took place on April 20, 2010, chaos and uncertainty in the zone had generally subsided and individuals had returned—or were on their way to returning—to more stable lives. Thus, the *Deepwater Horizon* oil spill reintroduced an element of uncertainty to people's lives (Osofsky and Osofsky 2013). Hence, it is not an easy task to ascertain whether the mental health effects observed in Gulf of Mexico (the Gulf) residents are specifically due to the *Deepwater Horizon* spill or remnants from Katrina disaster (cumulative effects from both catastrophes).

Thus, Osofsky, Palinkas, and Galloway (2011) assessed mental health effects in coastal residents considering their previous experience with Hurricane Katrina. The greatest influence on mental well-being obtained was the extent of disruption that the oil spill created in participants' lives, work, family, and social engagement. This resulted in increased symptoms of anxiety, depression, and posttraumatic stress, reporting frequencies in residents well above the national prevalence rates. Resilience (ability to rebound after experiencing adversity) was found to play an important role in mental well-being; data suggested that individuals who survived Hurricane Katrina believed that they learned from experience and were able to adapt to and cope with adversity.

More recently, Cherry et al. (2015) compared current coastal residents with severe property damage from the 2005 hurricanes Katrina and Rita, and exposure to the 2010 *Deepwater Horizon* oil spill, with former coastal residents and an indirectly affected control group (non-coastal residents who lived at least 80 miles outside of the storm-devastated areas of south Louisiana), in order to assess long-term psychological outcomes after the disasters and possible relationships to religiosity and social support. Their results showed that people who experienced recent and severe trauma related to natural and technological disasters were at risk for adverse psychological outcomes in the years after these events. Greater risk was observed in those individuals with low income, low social support, and high levels of nonorganizational religiosity.

In a study conducted to assess the psychological impact on children and their families residing in the Gulf Coast, data demonstrated that more than one-third of children experienced either mental health distress or physical symptoms, as reported by their parents (Abramson et al. 2010). Further, more than one-quarter of coastal residents thought they might need to move away from the area because of the oil spill.

Grattan et al. (2011) examined residents of fishing communities directly exposed to coastal oil or indirectly impacted to assess early mental health effects and perceived risk while the spill was still in progress. It was found that residents of both communities displayed clinically significant differences in depression and anxiety, whereas no marked differences between community groups were observed in terms of psychological distress, adjustment, neurocognition, or environmental worry. Further, participants with spill-related income loss had significantly worse scores than those with stable income on anxiety, depression, fatigue, confusion, and total mood disturbance scales, while there were higher rates of depression, less resilience, and more likelihood of using behavioral disengagement as a coping strategy. Analysis of this same exposed cohort 1 year after the spill noted no significant change in levels of anxiety or depression, particularly for people who continued to sustain spill-related income loss (Morris et al. 2013).

The mental health status of coastal residents in Alabama and Mississippi Gulf Coast counties 4.5–5 months following the spill was assessed by Buttke et al. (2012a) using a cluster sampling methodology. Overall, the proportion of mentally or physically unhealthy days, days of limited activity in the previous 30 days, and symptoms of depression were greater within all sampling areas as compared with state annual estimates, although differences were not statistically significant in Alabama, likely due to the lower survey completion rates in that state. A follow-up of the same populations was carried out 1 year later by Buttke et al. (2012b), and data obtained suggested that mental health symptoms (depressive symptoms and anxiety disorder) in the Gulf Coast counties of Alabama and Mississippi were lower in 2011 than in months immediately following the oil spill, but the proportion of individuals with mental health symptoms was still higher than state and nationwide estimates. In addition, both studies noted significantly worse mental health parameters in those individuals who self-reported decreased income following the oil spill.

A comparison of the social and mental health impacts of the 1989 *Exxon Valdez* oil spill and the 2010 *Deepwater Horizon* oil spill—both occurred in U.S. territory—was carried out by Gill, Picou, and Ritchie (2012). A standardized indicator of event-related stress in random samples of residents of Cordova, AK, and south Mobile County, AL, collected 5 mo after each event was used. The analysis revealed similarly high levels of initial

psychological stress in the two populations. Family health concerns, commercial ties to renewable resources, and concern regarding economic future, economic loss, and exposure to the oil were the most reliable predictors of stress. Evidence indicated that on the basis of *Exxon Valdez* previous results, social disruption and psychological stress might characterize residents of Gulf Coast communities for decades to come.

Community attachment is usually thought to be associated with a variety of better outcomes for subjects—including better individual well-being and more positive affective states—because of social, emotional, and informational resources that such attachment typically entails (Berkman et al. 2000). Nevertheless, a study carried out by Lee and Blanchard (2012) to evaluate negative affective states in Gulf Coast residents showed that community attachment was associated with higher levels of negative responses, not only for households tied to the fishing, seafood, or oil industries, but also for those possessing no immediate link to either industry. Hence, although community attachment is essential for community resilience, it may also be disruptive to individual well-being when technological disasters occur in communities dependent on renewable and natural resources.

A group of mental health clinicians employed by Project Rebound and counselors from two school districts on the Gulf Coast were questioned 1 year after the spill to determine various mental health-related outcomes on the two communities. Analysis of the first interviews revealed that 1 year later communities were still in recovery (Werner and Locke 2012). Emotional and psychological symptoms were declining and more individuals were working, but families were still experiencing chronic stressors and disruption. Most of the disruption was related to job loss and changes in economic conditions. The second interviews aimed to describe the interactions of the participants with individuals requiring a wide range of mental health services after the disaster, and the role of stigma related to help-seeking behavior, since mental health services are only as helpful as the degree to which prospective clients accept and participate in them (Locke and Werner 2013). Observations collected demonstrated the existence of a number of stigma-related barriers to delivering services, including self-stigma, public stigma, and cultural implications of seeking and receiving aid. On the basis of their findings, Locke and Werner (2013) proposed five lessons to be integrated when rural communities commence to prepare for future disasters, with creative approaches to connect with the communities that will be the target of mental health services.

Physical/Physiological Effects

Studies published on physical/physiological effects of exposure to oil spills up to 2009 analyzed *Braer, Sea Empress, Nakhodka, Erika, Prestige*, and *Tasman Spirit* oil-exposed populations. Broad-spectrum acute health symptoms evaluated included respiratory problems, irritations (dermal, eyes, and throat), neurological effects (headache, nausea/vomiting/dizziness), and trauma-related symptoms (backpain, injuries). In general, higher prevalence of these symptoms was reported in the exposed groups, and related to the intensity of exposure (estimated as distance to the spill site, and time of participation in the cleanup work) (reviewed in Aguilera et al. 2010). Subsequent studies were collected and are presented in Table 3.

Prestige

Respiratory health in fishers highly exposed to *Prestige* oil spill and nonexposed controls was evaluated in three different studies conducted by the same research group 2, 5, and 6 years after cleanup, published after 2009. In the first, Rodríguez-Trigo et al. (2010) determined a number of respiratory clinical markers, and data showed persistent respiratory symptoms with elevated markers of airway injury in breath condensate related to participation in cleanup labors. Moreover, the risk for increased levels of different markers seemed to rise with exposure intensity.

In the second study (Zock et al. 2012), 5 years after exposure, respiratory symptoms were assessed by means of a questionnaire and compared to results obtained by these authors 12–24 months after the spill reporting increased risk of low-respiratory-tract symptoms (including wheeze, shortness of breath, cough and phlegm)

Table 3. Epidemiological studies on physical/physiological effects (different from genotoxicity, immunotoxicity and endocrine toxicity) related to exposure to oil spills published since 2009 (ordered by the chronology of the spills).

Accident and reference	Study characteristics	Methods	Results
Prestige—Rodríguez-Trigo et al. (2010)	Cross-sectional, 2 years after the exposure. Respiratory effects in fishers highly exposed (n = 501) and not exposed (n = 177).	Questionnaire on participation in cleanup activities. Respiratory symptoms, forced spirometry, MBPT, markers of oxidative stress, airway inflammation, and growth factor activity in exhaled breath condensate.	Participation in cleanup was associated with persistent respiratory symptoms and elevated markers of airway injury in breath condensate. The risk for elevated levels of exhaled 8-isoprostane, vascular endothelial growth factor, and basic fibroblast growth factor seemed to increase with intensity of exposure to cleanup work.
Prestige—Zock et al. (2012)	Cross-sectional, 5 years after cleanup. Persistence of respiratory symptoms in exposed fishers (n = 466) and nonexposed individuals (n = 156).	Questionnaire on participation in cleanup activities. Questionnaire on upper- and lower-respiratory-tract symptoms, allergic conditions, anxiety, and beliefs about the effects of the oil spill on the participant's own health.	The prevalence of lower-respiratory-tract symptoms had slightly decreased in both groups, but remained higher among the exposed. The risk of having persistent respiratory symptoms increased with the degree of exposure for moderately and highly exposed, when compared with those without any symptoms. Findings for nasal symptoms and for respiratory medication usage were similar.
Prestige—Zock et al. (2014)	Cross-sectional. Four-year follow-up, 6 years after cleanup work, and comparison with previous evaluation (Rodríguez-Trigo et al. 2010). Persistence of functional and biological respiratory health effects in never-smoking fishers exposed (n = 158) and nonexposed (n = 57) to the oil.	Questionnaire on participation in cleanup activities. Respiratory symptoms, forced spirometry, MBPT, markers of oxidative stress, airway inflammation, and growth factor activity in exhaled breath condensate.	During the 4-year follow-up period lung function, bronchial hyperresponsiveness, and the levels of respiratory biomarkers of oxidative stress and growth factors had deteriorated notably more among nonexposed than among exposed subjects. At follow-up, respiratory health indices were similar or better in cleanup workers than in nonexposed. No clear differences between highly exposed and moderately exposed cleanup workers were found.
Tasman Spirit—Meo et al. (2009a)	Cross-sectional. Health complaints among males involved in cleanup operations (n = 50) and controls (n = 50).	Standardized questionnaire on respiratory and general health complaints.	Subjects involved in oil cleanup operations had significantly higher rates of health complaints, including cough, runny nose, eye irritation/redness, sore throat, headache, nausea, and general illness, compared to their matched controls.
Tasman Spirit—Meo et al. (2009b)	Cross-sectional. Lung function in subjects exposed to crude oil spill into seawater (n = 31) and controls (n = 31).	Spirometry.	Subjects exposed to polluted air for periods longer than 15 d showed a significant reduction in FVC, FEV1, $FEF_{25-75\%}$ and MVV.
Hebei Spirit—Kim et al. (2009)	Cross sectional, 2–3 mo after the spill. Health effects of exposure to BTEX in pregnant women (N = 80) from the Taean area.	Questionnaire survey to look for health effects. BTEX exposures were estimated using the CALPUFF dispersion model.	Pregnant women who lived near the accident site reported more symptoms of eye irritation and headache than those who lived farther from the site. There was a trend of decreasing symptoms with an increase in distance from the spill site. Pregnant women exposed to higher ambient cumulative levels of xylene were significantly more likely to report symptoms of skin and abdominal pain.
Hebei Spirit—Lee et al. (2009)	Cross-sectional. Protective effects of wearing protective devices on exposure and symptoms among the residents (n = 288) and volunteers (n = 724) who participated in the cleanup.	Questionnaires about symptoms, use of protective devices, and potential confounding variables. Urinary metabolites of VOC, PAH, and heavy metals.	Levels of fatigue and fever were higher among residents not wearing mask than among those who did wear mask. Urinary mercury levels were found to be significantly higher among residents not wearing work clothes or boots.

(*Continued*)

Table 3. (Continued).

Accident and reference	Study characteristics	Methods	Results
Hebei Spirit —Sim, Jo, and Song (2010)	Cross-sectional. Acute health problems in people engaged in the cleanup (N = 846).	Questionnaire on demographics, operation information, exposure to oil, and health status.	Residents and volunteers experienced acute health problems, such as back pain and skin lesions. More frequent and greater exposure (including lack of protective suit and mask) was strongly associated with a higher occurrence of symptoms.
Hebei Spirit —Cheong et al. (2011)	Cross-sectional. Physical symptoms in residents participating in cleanup work (n = 288) and nonexposed inland residents (n = 39).	Questionnaire regarding subjective physical symptoms (self-reported), sociodemographic characteristics, and cleanup activities. Urinary metabolites of VOC, PAH, and heavy metals.	Exposed residents showed associations between physical symptoms and the exposure levels defined in various ways (days of work, degree of skin contamination, and levels of some urinary metabolites of VOC, PAH, and metals), although no major abnormalities in urinary exposure biomarkers were observed.
Hebei Spirit —Na et al. (2012)	Cross-sectional, follow-up of the previously analyzed population (Sim, Jo, and Song 2010) 1 year later. Health problems of people involved with cleanup efforts (N = 442).	Questionnaire on demographic information, risk factors, and the continuation and duration of any health symptom.	Eye symptoms, headaches, skin symptoms, and neurovestibular symptoms had a longer duration than did back pain or respiratory symptoms.
Hebei Spirit —Ha et al. (2012)	Cross-sectional. Exposure status and acute health effects on volunteers who participated in the cleanup (N = 565).	Questionnaire regarding physical symptoms. Urinary metabolites of VOC and PAH before and after exposure.	Volunteers who participated for longer cleanup work reported an increase in physical symptoms (visual disturbance, nasal and bronchus irritation, headaches, heart palpitations, fatigue and fever, memory and cognitive disturbance, and abdominal pain). The levels of *t,t*-muconic acid, mandelic acid, and 1-hydroxypyrene were significantly higher in samples after cleanup than those measured before participation.
Hebei Spirit —Jung et al. (2013)	Cross-sectional, 1.5 years after the accident. Respiratory effects on children who lived along the Yellow Coast (N = 436).	Modified International Study of Asthma and Allergies in Childhood questionnaire. Health examination (skin prick test, pulmonary function test, and MBPT).	The children who lived close to the oil spill area showed a significantly lower FEV1, an increased prevalence of "asthma ever" (based on a questionnaire), and "airway hyperresponsiveness" (based on the MBPT) than those who lived far from the oil spill area. Male sex, family history of asthma, and residence near the oil spill area were significant risk factors for asthma.
Hebei Spirit —Noh et al. (2015)	Cross-sectional, 14–23 mo after the spill. Relationship between oil-spill exposure and oxidative stress in residents living near the affected area (N = 671).	Surrogates for exposure: total duration of cleanup work and levels of PAH urinary metabolites. Oxidative stress: urinary levels of MDA and 8-OHdG.	Levels of oxidative stress biomarkers were significantly increased with longer involvement in cleanup work over one year after the spill. The level of 1-OHP had a significant positive correlation with the total duration of cleanup work involvement. Increasing levels of 1-OHP were significantly associated with increased MDA and 8-OHdG; the strength of association weakened as time passed since the last participation in cleanup work, but significance was maintained for up to 12 months

(*Continued*)

Table 3. (Continued).

Accident and reference	Study characteristics	Methods	Results
Deepwater Horizon—D'Andrea and Reddy (2013)	Cross-sectional. Adverse health effects in subjects participating in the cleanup activity (n = 117) and controls (n = 130).	Clinical data (WBC and platelet counts, hemoglobin, hematocrit, blood urea nitrogen, creatinine, ALP, AST, ALT) and somatic symptom complaints.	Platelet counts were significantly decreased, and hemoglobin and hematocrit levels were significantly increased, among oil-spill-exposed subjects. Oil-spill-exposed subjects had significantly higher levels of ALP, AST, and ALT compared with the unexposed subjects.
Deepwater Horizon—D'Andrea and Reddy (2014)	Cross-sectional. Hematological and liver function indices in subjects who participated in the cleanup operations (N = 117).	WBC and platelet counts, hemoglobin, hematocrit, blood urea nitrogen, creatinine, ALP, AST, ALT, and urinary phenol. Values were compared with the standardized normal range reference values.	None of the subjects had the upper limit of the normal range for WBC count, with a similar pattern for platelet counts and blood urea nitrogen levels. More than 70% of the subjects had creatinine levels toward the upper limit of the normal range and 23% of subjects had creatinine levels above the upper limit of the normal range. Hemoglobin and hematocrit levels were toward the upper limit of normal in more than two-thirds of the subjects. AST and ALT levels above the upper limit of normal were seen in 15% and 31% of subjects, respectively. More than 80% of subjects had urinary phenol levels higher than detectable levels.
Deepwater Horizon—Peres et al. (2016)	Cross-sectional. Association between exposure and physical health in women residing in southern Louisiana (N = 2,126).	Telephone interview on frequency of 13 physical health symptoms. Exposure was characterized as physical/environmental exposure and economic exposure.	Women exposed to the oil spill had significantly higher odds of several physical health symptoms, with the strongest associations estimated for burning in nose, throat, or lungs; sore throat; dizziness and wheezing. Some physical health symptoms (wheezing; watery, burning, itchy eyes; stuffy, itchy, runny nose; and headaches) were also associated with high economic exposure.
Deepwater Horizon—Schaum et al. (2010)	Screening-level assessment of the exposures and cancer risks posed by the dioxin emissions from in situ oil burns.	The potential cancer risk was calculated using upper estimates for the oil burn emission factor, modeled air and fish concentrations, and conservative exposure assumptions. U.S. Environmental Protection Agency (EPA) AERMOD model was used to estimate air concentrations in the immediate vicinity of the oil burns and National Oceanic and Atmospheric Administration (NOAA) HYSPLIT model to estimate more distant air concentrations and deposition rates.	The lifetime incremental cancer risks were estimated as 6×10^{-8} for inhalation by workers, 6×10^{-12} for inhalation by onshore residents, and 6×10^{-8} for fish consumption by residents. For all scenarios, the risk estimates represent upper bounds and actual risks would be expected to be less.

Note. Studies assessing both mental and physical parameters are included in ">Table 1. 1-OHP, 1-hydroxypyrene; 8-OHdG, 8-hydroxy-2-deoxyguanosine; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BTEX, benzene, toluene, ethylbenzene, and xylenes; $FEF_{25\%-75\%}$, forced expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MBPT, methacholine bronchial provocation test; MDA, malondialdehyde; MVV, maximum voluntary ventilation; PAH, polycyclic aromatic hydrocarbons; VOC, volatile organic compounds; WBC, white blood cell.

with time of exposure and number of cleanup activities performed (Zock et al. 2007). New observations indicated slight decrease of respiratory symptoms both in those exposed and in controls, but these manifestations still remained higher among the exposed, and were related to the degree of exposure. Therefore, Zock et al. (2012) concluded that participation in cleanup activities of oil spills may result in respiratory symptoms that persist up to 5 years after exposure.

The third study (Zock et al. 2014) was a 4-year follow-up of the first mentioned (Rodríguez-Trigo et al. 2010) investigation, aimed to determine the persistence of functional and biological adverse respiratory health effects observed 2 years after exposure, including a smaller cohort of nonsmoking individuals. Results revealed that clinical respiratory markers deteriorated notably less, and were similar or better, in those exposed than in controls; thus, no apparent chronic adverse respiratory health effects were noted in cleanup workers 6 years after exposure. In the discussion of these results, Zock et al. (2014) argued that nonexposed participants of the follow-up survey displayed more respiratory symptoms at the initial evaluation than nonexposed individuals who were lost to follow-up, indicating that unexposed fishers were more motivated to participate in the follow-up if they had been suffering respiratory problems. This may have resulted in a bias when comparing adverse respiratory health status at follow-up between exposed and controls, thus masking the possible persistence of respiratory effects.

Tasman Spirit

Different aspects of respiratory and general health were also analyzed by Meo et al. (2009a; 2009b) in individuals exposed to the *Tasman Spirit* oil spill and controls. Subjects involved in cleanup operations showed a higher rate of health complaints related to cough, runny nose, sore throat, general illness, eye irritation/redness, nausea, and headache, compared to controls (Meo et al. 2009a). Exposure duration longer than 15 days was associated with adverse effects on lung functions (significant reductions in spirometry parameters) (Meo et al. 2009b).

Hebei Spirit

Most studies carried out in population exposed to *Hebei Spirit* oil spill that assessed physical health symptoms used questionnaires to collect this information. Thus, Lee et al. (2010) determined acute health effects in residents from coastal villages, classifying them according to degree of contamination in heavily, moderately, or lightly oil-soaked areas. Data demonstrated significantly increased risk of several physical symptoms (headache, nausea, dizziness, fatigue, tingling of limb, hot flushing, sore throat, cough, runny nose, shortness of breath, itchy skin, rash, and sore eyes) in residents from heavily and moderately oil soaked areas compared to those from lightly contaminated areas.

Residents exposed to oil through cleanup work during the *Hebei Spirit* oil spill also showed associations between subjective physical symptoms (self-reported, including visual disturbance, nasal, dermal and bronchial irritation, sore throat, headache, palpitation, and nausea/vomiting) and exposure levels defined by days of work, degree of skin contamination, and concentrations of some urinary exposure biomarkers for volatile organic compounds (VOC), polycyclic aromatic hydrocarbons (PAH), and metals, although major abnormalities of urinary exposure biomarkers were absent (Cheong et al. 2011).

Similarly, volunteers participating for longer durations in the cleanup of the *Hebei Spirit* oil spill demonstrated several increased frequency of physical symptoms, including visual disturbances, nasal and bronchus irritation, headaches, heart palpitations, fatigue and fever, memory and cognitive disturbances, and abdominal pain (Ha et al. 2012). Analyses of urinary levels of some VOC and PAH metabolites revealed significantly higher values after cleanup operations than before, although no marked associations were noted between physical symptoms and elevated urinary levels due to cleanup efforts (with the exception of dermal irritation and *t,t*-muconic acid), which indicated this may be partially due to lack of statistical power.

Acute health symptoms were also analyzed in subjects engaged in the *Hebei Spirit* oil spill cleanup for relatively short periods of time (7–14 days), mostly residents and volunteers (Sim, Jo, and Song 2010). Symptoms were classified into six categories: back pain, skin lesions, headache, and eye, neurovestibular, and respiratory symptoms. The manifestations most frequently reported in people exposed to the oil were respiratory, back pain, headache, and neurovestibular. As in previously mentioned studies, risk analyses revealed that more frequent and greater exposure

was strongly associated with a higher occurrence of symptoms, and that lack of protective equipment and safety education was positively associated with acute adverse health effects.

The specific protective influence of wearing personal protective equipment (work clothes, mask, filter mask, gloves and boots) on exposure (determined by analysis of urinary metabolites of VOC, PAH, and heavy metals) and physical symptoms was also examined by Lee et al. (2009) in volunteers and residents participating in *Hebei Spirit* oil spill cleanup. Volunteers, who usually participated for about 1 day in the cleanup, used protective devices more often than residents, who participated in the cleanup work for a longer period. Those residents who did not wear a mask complained of fatigue and fever fivefold more than those who did wear it. Using protective equipment did not influence the levels of urinary VOC and PAH biomarkers, but those residents who did not wear work clothes or boots displayed significantly higher mercury urinary concentration than those who did wear them.

Regarding possible effects on subgroups of especially susceptible subjects, Kim et al. (2009) evaluated a specific cohort of pregnant women from the Taean area, estimating also exposure to VOC with a dispersion model. Higher rates of symptoms of eye irritation and headache were reported by pregnant women who lived near the accident site than by those residing farther away. Indeed, there was a trend of decreasing symptoms with a rise in distance from the spill site.

Another particularly sensitive cohort studied by Jung et al. (2013), determining respiratory function markers, was children who lived close to the oil spill area, where more asthmatic symptoms, increased impaired lung function, and elevated prevalence of bronchial hyperreactivity occurred compared to those who resided far from the oil spill area. Living close to the oil spill area was reported to be a risk factor for asthma, together with male gender and family history of this disease.

Persistence of acute adverse health problems in individuals involved with the cleanup operation of the *Hebei Spirit* oil spill was assessed by Na et al. (2012), in a follow-up of the population previously analyzed by Sim, Jo, and Song (2010). One year after the exposure, skin lesions, headaches, eye manifestations, and neurovestibular symptoms correlated with the oil spill cleanup operation, which displayed a relatively longer duration than back pain or respiratory symptoms. Notably, females experienced longer periods of headaches, and subjects whose daily participation in cleanup efforts exceeded 8 h showed a longer duration of eye symptoms.

Finally, not acute symptoms but oxidative stress biomarkers in long-term participants in cleanup work after the *Hebei Spirit* oil spill were reported by Noh et al. (2015) more than 1 year after the accident. Oxidative stress was measured using urinary levels of levels of malondialdehyde and 8-hydroxy-2′-deoxyguanosine, indicators of lipid peroxidation and oxidative DNA damage, respectively. Levels of oxidative stress biomarkers showed significant positive associations with total cleanup work duration and urinary level of 1-hydroxypyrene (biomarker of PAH exposure) up to approximately 12 months after the last cleanup.

Deepwater Horizon

Apart from the devastation produced in the same area by Hurricane Katrina 5 years before, another circumstance that makes the Gulf oil spill unique is the large-scale use of dispersants to break up the oil slick. By late July 2010, more than 1.8 million gallons of dispersant—which contained detergents, surfactants, and petroleum distillates, including respiratory irritants—had been applied in the Gulf (Solomon and Janssen 2010). Several recent studies highlighted the potential human health toxicity associated with the Corexit 9500A dispersant used during the Gulf oil spill, namely, immunotoxicological (Anderson et al. 2011), cytotoxicity (Shi, Roy-Engel, and Wang 2013), acute cardiovascular (Krajnak et al. 2011), pulmonary (Roberts et al. 2011), and neurotoxic effects (Sriram et al. 2011). It should be noted that the *Deepwater Horizon* oil spill affected not only humans but also the marine ecosystem health and functionality (Brewton, Fulford, and Griffitt 2013)

Moreover, in an attempt to elucidate the molecular mechanisms involved in the effects of oil and oil dispersants on the respiratory system, Liu et al. (2015) carried out a transcriptomic profile study

and found 26 differentially expressed genes in human airway epithelial cells grown under treatment of crude oil—alone or in combination with dispersants—compared to controls. These genes were reported to be involved in important pathological features observed in common lung diseases, such as asthma, cystic fibrosis, and chronic obstructive pulmonary disease, thus providing mechanistic insights into the detrimental effects of oil and oil dispersants on the respiratory system.

The National Institute for Occupational Safety and Health (NIOSH) investigated potential acute health effects associated with a wide range of offshore and onshore Gulf of Mexico oil spill response work activities (King and Gibbings 2011), considering not only chemical exposures (from oil components, dispersant components and in situ burns) but also heat stress (due to weather conditions and the use of personal protective equipment). Nonspecific symptoms such as headache, eye and respiratory irritation, and fatigue were more commonly reported by responders who self-reported exposures to oil, dispersants, or other chemicals compared to workers who self-reported no such exposures.

Adverse health effects of the Gulf of Mexico oil spill were also investigated by D'Andrea and Reddy (2013) in subjects participating in cleanup activities and controls, assessing hematologic and hepatic markers and somatic symptom complaints. Clinical alterations found in exposed subjects included decreased platelet counts and increased levels of levels of hemoglobin, hematocrit, and serum hepatic enzymes compared to controls. The most reported somatic symptoms were headache, shortness of breath, skin rash, cough, fatigue, painful joints, and chest pain. The same hematological and liver function clinical parameters in the exposed group were subsequently compared with the standardized normal range reference values (D'Andrea and Reddy, 2014). As a result of the anomalies detected in the comparisons, data obtained indicated that subjects exposed were at risk of developing alterations in hematological profile and liver function.

More recently, Peres et al. (2016) assessed physical health symptoms in a large group of women residing in southern Louisiana, by means of telephone interviews. To characterize the exposure to the oil spill, Peres et al. (2016) used the Exposure Status Scale developed by Palinkas et al. (1993) and added further questions on the financial impact of the oil spill and the participant's ability to smell the oil. After evaluating all exposure-related data, a two-factor solution was identified as the best fit for the data; these factors were labeled as "physical/environmental exposure" and "economic exposure." High physical/environmental exposure was significantly associated with all of the physical health symptoms, with the strongest associations for burning in nose, throat, or lungs; sore throat; dizziness; and wheezing. Further, women who had high economic exposure were significantly more likely to report wheezing; headaches; watery, burning, itchy eyes; and stuffy, itchy, runny nose.

In situ oil burns were conducted for the management of oil spilled after the *Deepwater Horizon* explosion. Assessment of the exposures and risks posed by the dioxin emissions from these fires was modeled by Schaum et al. (2010), considering three different scenarios. The lifetime incremental cancer risk was estimated as 6×10^{-8} for inhalation by workers, 6×10^{-12} for inhalation by onshore residents, and 6×10^{-8} for fish consumption by residents. For all scenarios, the risk estimates represent upper bounds, and actual risk would be expected to be less.

Genotoxicity, Immunotoxicity, and Endocrine Toxicity

All studies published since 2009 to date regarding genotoxicity, immunotoxicity, and endocrine toxicity were carried out on *Prestige* oil-exposed populations (Table 4). In this section studies were classified according to the type of toxicity assessed.

Genotoxicity

Previous investigations related to the *Prestige* accident noted significant increases in different genotoxicity parameters in subjects involved in autopsies and cleaning of oil-contaminated birds (Laffon et al. 2006) and in volunteers and hired workers participating in cleanup tasks (Pérez-Cadahía et al. 2006; 2007; 2008a; 2008b; 2008c) with regard to the corresponding control groups

Table 4. Epidemiological studies on genotoxicity, immunotoxicity, and endocrine toxicity related to exposure to oil spills published since 2009

Accident and reference	Study characteristics	Methods	Results
Prestige—Rodríguez-Trigo et al. (2010)	Cross-sectional, 2 years after the spill.	Chromosomal lesions and structural chromosome alterations in circulating lymphocytes.	A higher proportion of exposed participants had structural chromosomal alterations, predominantly unbalanced alterations.
	Chromosomal damage in fishers highly exposed (n = 91) and not exposed (n = 46).		The risk for structural chromosomal alterations seemed to increase with intensity of exposure.
Prestige—Monyarch et al. (2013)	Cross-sectional, 2 years after the spill.	Chromosomal aberrations in banded preparations, and DNA repair efficiency with aphidicolin, in peripheral blood samples.	The chromosomal bands 2q21, 3q27, and 5q31, commonly involved in hematological cancer, were mostly affected by acute oil exposure. The dysfunction in DNA repair mechanisms, expressed as chromosomal damage, was significantly higher in oil-exposed participants than in those not exposed.
	Analysis of chromosomal lesion locations in fishers highly exposed (n = 91) and not exposed (n = 46), and DNA repair efficiency in exposed (n = 14) and not exposed (n = 14) individuals.		
Prestige—Biern et al. (2015)	Cross-sectional, 2 years after the spill.	Chromosome lesions, structural chromosome alterations, and cytokinesis-block MN test (MN, nucleoplasmic bridges and nuclear buds frequencies) in peripheral blood samples.	No significant differences were found between exposed and nonexposed individuals for any MN test parameter evaluated.
	Genotoxicity in fishers highly exposed (n = 20) and not exposed (n = 20) individuals.		Chromosome lesions, but not structural chromosome alterations, were higher in exposed than in nonexposed individuals.
Prestige—Hildur et al. (2015)	Cross-sectional, follow-up 6 years after the exposure.	Chromosome lesions and structural chromosome alterations in circulating lymphocytes.	No significant statistical differences were observed between exposed and nonexposed individuals for chromosome lesions or structural chromosome alterations.
	Chromosomal damage in fishers exposed (n = 52) and not exposed (n = 23), already analyzed in Monyarch et al. (2013).		Unexpectedly, an increase in structural chromosome alterations in nonexposed individuals was detected 4 years after the initial study.
Prestige—Laffon et al. (2013)	Cross-sectional, follow-up 7 years after the exposure.	Prolactin and cortisol plasma concentrations, percentages of lymphocyte subsets, plasma levels of circulating cytokines, and serum concentrations of neopterin, tryptophan, and kynurenine.	Significant differences in exposed individuals vs. referents were observed in cortisol (increase), kynurenine, and % $CD16^+56^+$ lymphocytes (both decrease). Effect of using protective mask was observed on neopterin, $\%CD8^+$ cells, $CD4^+/CD8^+$ ratio, and interleukin 4.
	Endocrine and immunological alterations in individuals exposed for at least two months (n = 54) and controls (n = 50).		
Prestige—Laffon et al. (2014)	Cross-sectional, follow-up 7 years after the exposure.	Comet assay, TCR mutation assay, MN test (both cytokinesis-block test and flow cytometry) in peripheral blood samples.	No significant differences were obtained between the exposed and the controls in the comet assay, the TCR mutation assay, and the cytokinesis-block MN test.
	Genotoxic effects in individuals exposed for at least 2 mo (n = 54) and controls (n = 50).		

Note. MN, micronucleus; TCR, T-cell receptor.

(reviewed in Aguilera et al. 2010). Only one study reported no evidence of genotoxicity in residents exposed to the *Braer* oil spill who were examined 10 days, 10 weeks, and 1 year after the accident for DNA adducts and mutations at the *hprt* gene, as compared to the controls (Cole et al. 1997). However, the size of the two groups assessed in this case was extremely small (26 residents and 9 controls), thus hindering the possibility of producing statistically reliable conclusions. In addition, participation of the exposed individuals in the cleanup tasks was not specified; only their status as residents in the polluted area was mentioned, but no indication of absolute or relative level of their exposure was provided. Hence, it may well be that those who participated in the *Prestige* cleanup were more severely exposed to the oil compounds than those who resided near the *Braer* spill but who did not carry out cleanup operations.

After 2009, a study conducted by Rodríguez-Trigo et al. (2010) analyzed highly exposed fishers who participated in the cleanup of the coastal *Prestige* oil spill for at least 15 days and fishers who did not participate in cleanup activities, 2 years after the accident. Although no significant differences between exposed and nonexposed participants were observed for chromosomal lesions, a higher proportion of exposed participants had structural chromosomal alterations, primarily chromosomal imbalances (translocations, acentric fragments, deletions, and markers), dose-dependently related to some measure of intensity of exposure. A more thorough cytogenetic analysis of the chromosomal lesion locations noted in this population revealed three chromosomal bands commonly involved in hematological cancer as the most affected by acute oil exposure (Monyarch et al. 2013). These authors suggested that breakages in these bands might induce chromosomal instability, which may explain the increased risk of cancer (leukemia and lymphomas) reported in chronically benzene-exposed individuals (Escobar et al. 2007; Stillman, Varella-Garcia, and Irons 2000; Zhang, Eastmond, and Smith 2002). Further, in the same study DNA repair errors were assessed in lymphocyte cultures with aphidicolin (an inhibitor of DNA polymerase α and other polymerases), and significantly higher dysfunction in DNA repair mechanisms, expressed as chromosomal damage, was detected in oil-exposed participants compared to nonexposed participants.

The same research group analyzed a smaller subset of exposed and nonexposed fishers from the same sampling for nuclear anomalies (micronucleus [MN], nucleoplasmic bridges, and nuclear buds) and chromosome damage (Biern et al. 2015). No significant differences in frequencies of nuclear anomalies between exposed and nonexposed individuals were found but, as reported previously, chromosome damage in the same individuals was higher in exposed individuals, especially for chromosome lesions.

As a further confirmation of the results obtained in these epidemiologic studies, an in vivo study using a rat model of subchronic exposure to a fuel oil with characteristics similar to those of the oil spilled by the *Prestige* tanker was carried out by Valdiglesias et al. (2012), in order to determine potential genotoxic effects under strictly controlled exposure conditions. Results obtained indicated that oil exposure by inhalation induced DNA damage in rats, and alterations in DNA repair responses, although the sensitivity to oil substances varied depending on rat strain. These data supported previously described genotoxic effects in humans exposed to *Prestige* oil during cleanup tasks.

In order to determine the persistence of genotoxic alterations observed beyond a 2-year period, two follow-up studies were conducted. In the first, Hildur et al. (2015) determined chromosome damage in *Prestige* oil-exposed and nonexposed fishers examined previously (Biern et al. 2015; Monyarch et al. 2013; Rodríguez-Trigo et al. 2010), 6 years later. Even though no marked differences were observed between exposed and nonexposed individuals for chromosome lesions or structural chromosome alterations, comparison with data obtained 2 years after the exposure revealed lesion incidences similar to those previously found 4 years earlier. On this basis, Hildur et al. (2015) suggested that this appears to indicate that the cells of the bone marrow are affected, although evidence indicates also the possibility of some type of selection bias as a limitation of the study. Further, a surprising rise in chromosome damage in nonexposed individuals was found 6 years after *Prestige* spill versus those detected 2 years after the exposure, which was suggested to be an indirect exposure of these individuals to some oil compounds or other toxic agents during the last 4 years.

The second follow-up study was carried out 7 years after the *Prestige* accident and included individuals exposed to the oil for a mean of 9 months (range 2–10 months) and controls (Laffon et al. 2014). Primary DNA damage was assessed by means of the comet assay, mutagenicity by T-cell receptor (TCR) mutation assay—a reliable biomarker for long-term studies because it provides information regarding genotoxic effects that occurred several months to several years after exposure (Ishioka et al. 1997)—and MN frequency was determined both by the cytokinesis-block test and by flow cytometry. Results reported in this study demonstrated no evidence of persistence of genotoxic damage in individuals exposed to *Prestige* oil in any of the biomarkers analyzed, suggesting that bone-marrow hematopoietic stem cells do not necessarily display permanent damage in their DNA, as long as subjects remain exposure free for a period of time (7 years).

Immunotoxicity and Endocrine Toxicity

Only three studies were published before 2009 assessing immunotoxicity and/or endocrine toxicity parameters (Aguilera et al. 2010). Decreases in levels of hormones prolactin and cortisol, both markers of psychophysiological stress, were previously found in individuals exposed to the *Prestige* oil spill through participation in cleanup operations as compared to the controls, indicating alterations in the normal endocrine function in the individuals (Pérez-Cadahía et al. 2007; 2008a). Gestal et al. (2004) showed that individuals exposed to the same oil spill for several months had significant modifications in some lymphocyte subpopulations, as well as in concentrations of plasma cytokines, but no marked effects were detected in a group of short-term-exposed volunteers. Khurshid, Sheikh, and Iqbal (2008) found slight increases in lymphocyte and eosinophil levels in people working/living in the vicinity of the *Tasman Spirit* oil-polluted area.

Only one study was published after 2009 on specific determination of immunological and endocrine parameters in oil-spill-exposed individuals, a follow-up 7 years after the *Prestige* accident (Laffon et al. 2013). A number of immunological parameters (percent lymphocyte subsets, and circulating levels of several cytokines, neopterin, tryptophan, and kynurenine) and endocrine parameters (prolactin and cortisol plasma concentrations) were determined, and significant alterations were observed in the exposed subjects, namely, elevation in cortisol concentration and decrease in percent natural killer (NK) cells. Since cortisol suppresses the immune response, it may be that the overall fall in NK cells observed in the exposed group was an indirect consequence of increase in cortisol in those individuals. Significantly higher levels of plasma cortisol were previously reported in outdoor workers chronically exposed to urban pollution, which shares several compounds with oil (Rosati et al. 2011; Tomei et al. 2003), and a chronic rise in cortisol was established as associated with negative health outcomes (Rosati et al. 2011). It is worthwhile noting that the reduced number of NK cells might have serious consequences because these cells control several types of tumors and microbial infections by limiting their spread and subsequent tissue damage (Vivier et al. 2008).

Discussion

Previously reported results on the assessment of health effects in populations exposed to oil spills from the *Exxon Valdez, Braer, Sea Empress, Nakhodka, Erika, Prestige*, and *Tasman Spirit* tankers indicated higher rates of mental health parameters (depression, anxiety disorder, event-related psychological stress, and posttraumatic stress disorder), physiological health parameters (respiratory problems, irritations, neurological effects, and trauma-related symptoms), genotoxicity parameters, and alterations in levels of several hormones, lymphocyte subsets, and cytokines associated with exposure.

New studies published on oil-spill-exposed populations—residents or participants in cleanup operations—and gathered in this review provide additional evidence of adverse health effects related to exposure regarding different parameters in all the three categories considered. Data indicated that several symptoms may persist some years after exposure. While several of the oil spill studies focused on human health effects published before 2009 lacked appropriate comparison populations to determine whether the observed health symptoms were in excess of expectation, most of the newly published investigations on health effects related to exposure to oil spills include a comparison group: either nonexposed controls

(Biern et al. 2015; Cheong et al. 2011; D'Andrea and Reddy 2013; Hildur et al. 2015; Laffon et al. 2013; 2014; Meo et al. 2009a; 2009b; Monyarch et al. 2013; Rodríguez-Trigo et al. 2010; Zock et al. 2012; 2014), lightly exposed individuals (Grattan et al. 2011; Ha et al. 2013; Lee et al. 2010; Pérez-Pereira et al. 2012), statewide and nationwide reports (Buttke et al. 2012a), or the same individuals before the exposure started (Ha et al. 2012). Thus, results reported showing significant differences with regard to a reference group have increased reliability, although evident limitations in some of these studies are related to small population sizes or possible selection bias.

Although numerous investigations evaluated self-reported health symptoms (both mental health and physical health outcomes), which may be considered somewhat subjective, others were based upon analysis of objective clinical parameters, such as respiratory parameters (forced spirometry, methacoline challenge, markers of oxidative stress, airway inflammation and growth factor activity in exhaled breath condensate, and skin prick test for common inhalant allergens) (Jung et al. 2013; Meo et al. 2009b; Rodríguez-Trigo et al. 2010; Zock et al. 2014), hematological parameters (white blood cell and platelet counts, hemoglobin, hematocrit, blood urea nitrogen, creatinine, and liver enzymes) (D'Andrea and Reddy 2013, 2014), oxidative stress parameters (urinary levels of malondialdehyde and 8-hydroxy-2′-deoxyguanosine) (Noh et al. 2015), endocrine parameters (plasma prolactin and cortisol concentrations; Laffon et al. 2013), or immunological parameters (lymphocyte subsets and plasma cytokines) (Laffon et al. 2013).

Another important issue to be considered when determining the effects of oil spills for human health is exposure measurement. In the context of chemical incidents, exposure assessment has three basic objectives: (1) risk assessment, (2) definition of the populations at risk, and (3) providing exposure estimates for epidemiological studies (Bongers et al. 2008). The method of the self-report of exposure, estimating exposure according to the distance to the spill area or time involved in cleanup operations, is sensitive to bias. Conducting detailed exposure assessment has been strongly encouraged, since an accurate exposure assessment might make the difference between a study with conclusive results and a study with uncertainties leading to public unrest (Bongers et al. 2008; Savitz and Engel 2010). Exposure assessment using suitable biomarkers of the particular exposure (blood or urinary metabolites of VOC, PAH, and heavy metals) was carried out only in some studies on the *Prestige* oil spill (Pérez-Cadahía et al. 2007; 2008a; 2008c) and *Hebei Spirit* oil spill (Cheong et al. 2011; Ha et al. 2012; Lee et al. 2009; Noh et al. 2015).

Several studies concluded that 11–16% of the general population is substantially more vulnerable to toxic exposures than the remaining population (Caress and Steinemann 2004; 2005). However, the specific type of vulnerability varies from person to person and is unpredictable. Genetic variability in metabolizing genes and in DNA repair genes accounts for a certain part of this variability in the adverse effects produced by environmental chemicals (Park et al. 2004). Moreover, specific population sectors are especially more sensitive to chemical exposures due to their physiological characteristics, such as children, older adults, or pregnant women. Only a few oil spill studies focused attention on these groups: children's mental health effects (Abramson et al. 2010; Ha et al. 2013) or respiratory effects (Jung et al. 2013), and pregnant women's physiological symptoms (Kim et al. 2009), and the possible influence of metabolism or DNA repair genetic polymorphisms on health outcomes was exclusively analyzed after the *Prestige* accident (Laffon et al. 2006; Pérez-Cadahía et al. 2007; 2008a; 2008b). One needs to take into account that the "healthy worker" effect may be associated with consideration that emergency responders (volunteers and hired workers) are a little less vulnerable than the general population.

Health risks associated with exposure to oil spills tend to be even greater for volunteers, since they rush to the scene of the accident and are the first ones involved in the cleanup efforts, often with either scarce or inadequate or total absence of personal protective devices. Thus, considering the evidence provided regarding the many different health effects related to exposure to oil spills, protecting the health of emergency responders, professional and nonprofessional, is a daunting challenge in these disasters. In this regard, the influence of using personal protective equipment was scarcely evaluated thus far. Proper health-protection briefing was previously demonstrated to be associated with greater use of protective devices and consequently lower frequency of health problems in *Prestige* oil-exposed people

(Carrasco et al. 2006). Indeed, when absence of influence of using this equipment was unexpectedly found (Pérez-Cadahía et al. 2006; 2008b; 2008c), the incorrect use by individuals (motivated by not having received information on how to do it) was pointed out as a possible cause. Effectiveness of protective devices was more recently demonstrated since lower levels of fatigue and fever, and of urinary mercury, were recorded among *Hebei Spirit* spill area residents wearing mask and clothes or boots, respectively (Lee et al. 2009), and a higher occurrence of acute symptoms was associated with lack of protective suit and mask in subjects exposed to the same oil spill (Sim, Jo, and Song 2010). The effect of using a protective mask was observed for several immunological parameters in *Prestige* oil-exposed individuals even 7 years later (Laffon et al. 2013). Hence, although personal protective equipment markedly alters the body's ability to dissipate heat, thereby increasing water vapor pressure in the microenvironment under the equipment and leading to heat stress (Bishop, Gu, and Clapp 2000), their use is necessary to minimize risks associated with oil exposure.

The unpredictability of oil spill incidents requires that the logistic media are prepared to implement an immediate response, in terms of machinery and protective equipment availability, and organization and management of professional emergency responders and volunteer movements. In other words, in such emergency responses, there should be a previous phase for planning and preparedness, including appropriate contingency plans, which need to take place prior to incidents occurring (Bongers et al. 2008). Further, disaster management programs need to take into account general design and needs of health studies, such that many problems that may modulate health studies, including poor exposure assessment, may be prevented.

Conclusions

In the last decades, the number and size of accidental oil spills from tankers has decreased progressively (International Tanker Owners Pollution Federation Limited [ITOPF] 2015; Jernelöv 2010). In contrast, spills from aging, ill-maintained, or sabotaged pipelines have risen, and there is no clear trend with regard to blowouts (number of incidents or amount of spilled oil) (Jernelöv 2010). In addition, oil exploration and extraction are moving into ever-deeper water and into stormier and icier seas, increasing potential risk.

Once an oil spill accident occurs, usually a large number of people participate in the fight against contamination of the coastal environment and are in close contact with the oil: the "white tides" (thus named because of the color of the protective clothes) that combat the "black tides." It should be noted that residents of the shore areas affected by the spill are also directly or indirectly exposed to the oil chemicals and to the social and economic consequences of the spill. Hence, epidemiologic studies focused on risk evaluation need to consider all these parameters attributed to exposure to oil spills, whatever the source, as these are essential to thoroughly evaluate the possible effects for human health at different levels and to establish the proper preventive programs.

Previous and recently published studies provide abundant evidence to establish the relationship between exposure to oil spills and development of different types of adverse health effects in exposed individuals. Some of these studies reported a higher strength of symptoms in cleanup workers and community residents who were exposed more intensely and/or for longer periods of time, and the persistence of several alterations for several years. There is a lack of information regarding adverse health effects in especially susceptible groups, as well as on the role of personal protective devices, which needs to be addressed. Hence, health protection in these subjects should be a matter of concern. This does not only refer to time of exposure, since appropriate follow-up during long periods of time (years) hase been demonstrated to be necessary to guarantee early detection of any potential exposure-related effect.

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Review

Environmental Chemical Assessment in Clinical Practice: Unveiling the Elephant in the Room

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Abstract: A growing body of evidence suggests chemicals present in air, water, soil, food, building materials and household products are toxicants that contribute to the many chronic diseases typically seen in routine medical practice. Yet, despite calls from numerous organisations to provide clinicians with more training and awareness in environmental health, there are multiple barriers to the clinical assessment of toxic environmental exposures. Recent developments in the fields of systems biology, innovative breakthroughs in biomedical research encompassing the "-omics" fields, and advances in mobile sensing, peer-to-peer networks and big data, provide tools that future clinicians can use to assess environmental chemical exposures in their patients. There is also a need for concerted action at all levels, including actions by individual patients, clinicians, medical educators, regulators, government and non-government organisations, corporations and the wider civil society, to understand the "exposome" and minimise the extent of toxic exposures on current and future generations. Clinical environmental chemical risk assessment may provide a bridge between multiple disciplines that uses new technologies to herald in a new era in personalised medicine that unites clinicians, patients and civil society in the quest to understand and master the links between the environment and human health.

Keywords: environmental chemical assessment; exposome; clinical practice; toxicant; environmental medicine; personalized medicine; systems biology

1. Introduction

Human exposure to environmental chemicals has increased exponentially over the past decades and a growing body of evidence suggests that chemicals present in air, water, soil, food, building materials and household products are toxicants that contribute to many of the chronic diseases typically seen in clinical practice. Yet, despite the call from numerous organisations for regulatory reform and an increase in training on environmental health for clinicians, environmental chemical assessment is generally overlooked in clinical practice and environmental chemicals can be considered as an elephant in the room that is largely ignored.

The failure of genome-wide association studies to explain the vast majority of chronic diseases now afflicting 50% of people of working age [1], together with emerging research exploring aberrations in the epigenome and "exposome" (the total exposures seen during the organism's life) in the aetiology of chronic disease [2], has led to a paradigm shift in our understanding of chronic "non-communicable" disease [3]. Furthermore, the "epidemiological transition" from infectious diseases in developing countries to chronic diseases in developed countries, has led to a fundamental reconsideration of the health impact of environmental exposures [4].

Innovative breakthroughs in biomedical research and technology encompassing the emerging "-omics" fields (epigenomics, nutrigenomics, metabolomics, toxicogenomics), and advances in the field of classical toxicology, have further contributed to a new understanding of the relationship between chronic diseases and exposures to environmental chemicals across the lifespan. This new understanding validates what Hippocrates stated centuries ago; that one's diet, lifestyle and environment, has profound consequences on health and wellbeing [5], and has wide reaching ramifications for the practice of medicine that provides clinicians with unique and important roles to play in identifying and preventing environmental chemical exposures.

2. The Rise of Chemical Production and Exposures

The number of chemicals in the world is essentially unknown, yet the world's largest database on chemical information—the Chemical Abstracts Service (CAS) Registry^{SM} established in 1907, currently contains more than 100 million chemicals [6] with around 200,000 new chemicals being added each week [7]. While many of these chemicals are produced by natural processes, or are inadvertently produced as by-products of fossil fuel combustion or other industrial processes [8], the number of chemicals commercially produced has increased exponentially in parallel with increasing industrialization. Commercial chemical production has risen from 1 million tons in 1930 to 400 million tons in 2001 [9], and over the past few decades the global sale of chemicals has increased by a factor of 25 from U.S. $171 billion in 1970 to US$4.1 trillion in 2012 [10]. As of 2012, the number of industrial chemicals on the global market was estimated to be around 143,835 [10].

A number of large population biomonitoring studies have revealed widespread chemical exposures from the "womb to the tomb" with levels in humans and wildlife that are known to cause adverse health effects. Such studies include the National Health and Nutrition Examination Survey in the USA [11], DEMOCOPHES survey in Europe [12], German Environmental Surveys in Germany [13], Flemish Environment and Health Study in Belgium [14], Esteban cross sectional survey in France [15], Russian Federation [16] and the BIOAMBIENT ES in Spain [17] in addition to national birth cohort studies conducted in Denmark (Danish National Birth Cohort) [18], France (French Longitudinal Study of Children Survey) [19], Norway (Norwegian Mother and Child Cohort Study [20], and Spain (The Spanish Environment and Childhood Research Network) [21]. There are also ongoing epidemiological studies such as the Cross-Mediterranean Environment and Health Network project, which aim to demonstrate an integrated methodology for the interpretation of human biomonitoring data that will allow researchers to quantitatively assess the impact of chemical exposures on human health [16]. Despite these efforts, human toxicity data is lacking for most chemicals in widespread use, even when population-wide exposures are documented [22].

Disturbingly, many environmental chemicals are found in human breast milk and the placenta where they directly affect the foetus [23]. A landmark study conducted by the Environmental Working Group identified 287 chemicals in cord blood, raising the profile of the widespread exposures to everyday chemicals [24]. More recently, the Canadian "pre-polluted study" identified 137 chemicals in cord blood, 132 of which are reported to cause cancer and 133 that cause developmental and reproductive problems in mammals [25]. The brain of a foetus and infant is particularly vulnerable as the central nervous system is the dominant repository of foetal fat and many environmental toxicants are lipophilic. Consequently the health impact of chemical exposures is most evident in paediatric medicine where chronic disease has overtaken infectious diseases as the major burden of paediatric illness [26]. The obvious and extensive impact of environmental chemicals on children's health, has contributed to paediatrics being the first medical discipline to identify chemical exposures as an important health issue, with the American Academy of Paediatrics establishing an environmental health committee in 1958 and publishing its first edition of *Paediatric Environmental Health* for clinicians in 1999 [27].

While chemical exposure is ubiquitous in the general population, the Environmental Justice Hypothesis suggests that exposures are unevenly distributed. This hypothesis, which emerged

in the 1980s following the publication of several studies in the USA [28–32] suggests that environmental hazards are inequitably distributed according to class and race [33]. Yet, the strict bifurcation of communities into categories of Environmental Justice and Non-Environmental Justice is problematic [34], because much of the literature is based on comparisons of exposure and risk between different populations, rather than on the toxicological and biological impacts of those exposures [35]. Furthermore, while some minority groups and those with lower socioeconomic (SES) status are likely to bear a greater burden of environmental toxicants given their lifestyle, proximity to waste sites, industrial emissions and poorer quality ambient air, biomonitoring studies have identified toxicants in all individuals, the type and amount of which varies depending upon lifestyle factors and geographical variation. For example higher SES individuals have been found to have higher burdens of mercury, arsenic, caesium, thallium, perfluorinated compounds, certain types of phthalates and benzophenone-3 as a result of their lifestyle (fish consumption, dental history, homegrown vegies, cosmetic and sunscreen use) [36]. In contrast, lower SES individuals have been found to have higher levels of lead, cadmium, antimony, bisphenol-A and other types of phthalates, which may be partially mediated by smoking, occupation and diet [36].

3. Environmental Chemicals and the Origins of Chronic and Complex Disease

The dramatic rise in the number of commercially produced chemicals has resulted in exposure to industrial chemicals being ubiquitous in both developed and developing nations and an increasing disease burden that is not yet fully understood. The World Health Organisation estimates that 4.9 million deaths and 86 million Disability Adjusted Life Years were attributed to environmental chemicals in 2011 [10] and that approximately one-quarter of the global disease burden, and more than one-third of the burden among children under the age of 5 is due to modifiable environmental factors [37]. A recent review further estimated that the disease burden in the European Union associated with exposure to endocrine disrupting chemicals alone, cost $209 billion or 1.23% of Europe's GDP [38].

Many of the chronic diseases that have substantially increased in prevalence over the past 40 years, appear to be related in part to developmental factors associated with nutritional imbalance and exposures to environmental chemicals [39]. For example the "developmental obesogen" hypothesis is used to explain why the prevalence of obesity among school age children between the early 1970s and late 1990s has doubled or trebled [40]. Whilst obesity prevalence has begun to plateau, a growing number of chemical obesogens such as organochlorine pesticides [41–43], bisphenol A [44], PCBs and phthalates [45] have been found in-utero and are implicated in the development of obesity later in life [46,47].

The concept of early life origins of disease was first brought to light in 1934 by Kermack and colleagues who suggested that decreased death rates due to all causes were the result of improved childhood living conditions [48]. This was later expanded upon by Neel in 1962 [49], Forsdahl in the 1970s [50,51], and in the late 1980s by David Barker who associated nutritional deficits during fetal development and consequent low birth weight, to increased risks for obesity, diabetes and cardiovascular disease and thereby came to be considered as the father of the "Fetal Origins of Adult Disease" hypothesis [52]. Whilst the Developmental Origins of Health and Disease (DOHaD) has historically focused on nutrition, understanding of the role of early life experience in chronic disease aetiology requires an integrated analysis of all aspects of the environment (nutrition, psychosocial stress, drugs, microbiome and environmental pollutants) and how they interact to cause disease [53]. Thus, the DOHaD has far reaching implications in clinical practice, and implies a need for clinicians to undertake an extensive paediatric, environmental and occupational exposure history and consider the role of nutrition and environmental chemical exposures during critical windows of development to understand the development of chronic illness in later life.

The list of diseases that may be caused or exacerbated by environmental chemical exposures is extensive and growing. These diseases include diabetes [54,55], infertility [56–58], testicular dysgenesis syndrome [59,60] which encompasses hypospadias [61,62], cryptorchidism [63,64], testicular

cancer [65], and poor semen quality [66–68], ovarian dysgenesis syndrome [69], neurodegenerative diseases such as Alzheimer's Disease [70], respiratory disorders such as asthma [71] and chronic obstructive airway disease [72], as well as autoimmune diseases [8], obesity [73–75] and cardiovascular disease [76–78]. Emerging evidence is also linking industrial chemicals to a pandemic of neurodevelopmental disorders [79] the implications of which have devastating consequences on family's and the global economy [80,81]. Whilst the cause of these neurodevelopmental problems is not yet clear, genetic factors are acknowledged as only playing a minor role [82,83] and several hypotheses point to environmental influences involving aberrations in the gastrointestinal microbiota [83], industrial chemicals [81,84,85], malnutrition [86,87], viruses and drugs [88] as potential causal agents.

Environmental factors are also believed to account for a significant portion of cancer mortality worldwide [89]. There is a growing body of evidence associating various toxicants with cancer including: air pollutants like asbestos, radon, hexavalent chromium, tobacco smoke and benzo(a)pyrene with lung cancer [90–93]; endocrine disrupting chemicals such as pesticides, dioxins, furans and PCBs with an increased risk for breast cancer [94], endometrial, testicular and prostate cancer [95–98]; arsenic and disinfection by-products with bladder cancer [99,100]; vinyl chloride with liver cancer [101], benzene with leukemia [102]; and pesticides with childhood leukaemia [103–105]. Even though the incidence of cancer attributable to environmental chemical exposures has not been definitively established [106,107], the World Health Organization and the International Agency for Research on Cancer (IARC) suggest that between 7% and 19% of all cancers are attributable to toxic environmental exposures [108,109]. According to cancer biologists, this estimate is likely to be a gross underestimation, as many supposedly non-carcinogenic chemicals that are ubiquitous in the environment have been shown to exert low-dose effects that may contribute to carcinogenesis [110,111]. This is of particular concern in light of the fact that cancer has now become the world's leading cause of mortality [112].

Clinicians are also seeing a rise in the prevalence of patients with a shopping list of ongoing seemingly unrelated persistent complaints, which some have described as a "pandemic of idiopathic multimorbidity" [113]. While multimorbidity is associated with chemical sensitivity, it presents an increasingly common and confusing primary care dilemma often labelled as Chronic Fatigue Syndrome [114,115], Systemic Exertion Intolerance Disease [114], Sensitivity-Related Illness [116], Idiopathic Environmental Intolerances [117], Fibromyalgia [118], Electromagnetic Hypersensitivity [119], Sick Building Syndrome [120] and Multiple Chemical Sensitivity [114]. These conditions are diagnoses based on exclusion rather than any specific aetiology as they have no clear aetiology, pathogenesis, or recognised genetic or metabolic markers that can be observed with standard laboratory testing. Despite the fact that the degree of hypersensitivity often parallels the intensity of the total body burden of bio-accumulated toxicants [121], patients with these conditions are relatively understudied [122] and are frequently considered to have psychogenic illness. Such patients have complex needs, and frequently present with a multitude of health complaints in different organ systems that often require attention from a range of medical specialists [123]. It has been suggested that a common aetiological pathway for a diverse range of idiopathic environmental intolerances may involve environmental chemicals inducing oxidative stress and subsequent mitochondrial dysfunction [124,125], in addition to low-grade systemic inflammation in multiple organ systems [124,126], and polymorphisms in nitric oxide synthase [125], antioxidant and/or detoxification genes [116,124], that result in a "toxicant-induced loss of tolerance" [127,128]. It is further suggested that exposures occurring during critical windows of development play an important role and that early life exposures are significant contributors to chronic diseases throughout the lifespan and across generations [96,129].

4. Chemical Risk and Chemical Risk Assessment

In contrast to the great majority of acute conditions and infectious diseases where cause and effect can easily be established, exposure to low levels of thousands of environmental chemicals over a life

span requires a paradigm shift in the way in which causality is established. Chemical risk is based on the type and dose of chemical, combination effects, the timing of exposure, and individual risk factors, yet the existing chemical risk assessment framework only involves hazard identification and exposure assessment [130], where hazard identification assesses the ability of a chemical to cause harm at various dosage levels, and exposure assessment evaluates the dose that might be received at target tissue after contact. Such assessments rely heavily on data extrapolated from human epidemiology, animal testing and cell culture/*in vitro* laboratory studies [131] that fail to account for multiple routes of exposure, mixture effects, transgenerational epigenetic effects or individual human risk factors such as age, gender, genetics, nutrition, psychosocial determinants and comorbidities [130,132–134].

4.1. Dose Response and Low Dose Effects

Dose-response relationships follow the path laid by epidemiologist, Sir Austin Bradford Hill, and form the basis of most contemporary systems for chemical risk assessment and causation analysis [135]. Such assessments involve giving increasing levels of an individual chemical to a group of test animals with the key objective of providing a dose-response assessment that estimates a point of departure (traditionally the no-observed-adverse-effect (NOAEL) level or the lowest-observed-adverse-effect level), which is then used to extrapolate the quantity of substance above which adverse effects can be expected in humans [110]. Endocrine disrupting chemicals pose a particular dilemma for chemical risk assessment as these chemicals can exhibit non-monotonic dose-responses whereby the effect of low doses cannot be predicted by the effects observed at high doses [110,136]. In addition to the complexities involved with endocrine disruption, carcinogenesis is a highly complex process and a growing number of scientists are questioning the use of linear dose-response models for classifying carcinogens, as these models do not account for the complex and permutable pathogenesis of many cancers [137].

4.2. Chemical Mixtures and "Something from Nothing" Effects

The prediction of health risks based on NOAEL not only fails to account for non-monotonic dose-responses, it also fails to reflect real-life exposures which typically involves exposure to multiple chemicals [138]. This may explain why pesticide formulations such as "Roundup" have been shown to be significantly more toxic than their active principle (glyphosate), due to the inclusion of adjuvants that increase their potency yet are not accounted for in safety assessments [139]. Furthermore, the NOAEL approach does not consider "something from nothing" mixture toxicity whereby unpredictable additive, antagonistic or synergistic adverse effects may occur at doses around, or below points of departure [140]. For example, carpenters exposed to formaldehyde, terpenes and dust particles below their point of departure are reported to exhibit dyspnea, nose and throat irritation, chest tightness and productive cough [141] and complaints of headache, skin, eye, nose and throat irritation are reported in painters despite airborne exposure levels being below the known irritation levels for the single chemicals [142]. Similarly, weakly oestrogenic chemicals that are too small to be detected individually can jointly increase the actions of potent, endogenous sex steroids [143] and chemical mixtures can act synergistically to exert pro-carcinogenic and anti-carcinogenic effects that contribute to the accumulation of somatic mutations and instigate the hallmarks of cancer [110,144,145]. Inorganic arsenic is one such example. At high levels in drinking water, arsenic is a well-established human carcinogen associated with bladder, lung and skin cancer [146], however at lower doses, its cancer risk may depend upon other variables such as smoking, and on differences in individual susceptibility, either genetically based or via nutritional status or other conditions [147]. This observation parallels the well-established finding that smokers exposed to asbestos have a significant increase in lung cancer risk compared to non-smokers [148].

One theory of how chemical mixtures may elicit unexplained effects, is based on the observation that mixture effects commonly occur when chemical mixtures contain at least one lipophilic and one hydrophilic chemical [132]. Lipophilic chemicals promote the permeation of hydrophilic chemicals

through mucous membranes [132]. This is important because lipophilic barriers in the body (skin and mucous membranes) serve as the body's primary protection against the absorption of environmental chemicals [149]. The octanol-water partition coefficient, or K_{ow}, which classifies the lipophilic character of a given chemical, is a useful parameter for environmental risk assessment that is used extensively by authorities in the European Union [150]. Most lipophilic toxicants can permeate the body's membranes, and lipophilic chemicals with a K_{ow} greater than 2, are frequently used by the cosmetic industry as chemical penetration enhancers, as adjuvants in pesticides to increase the solubility of the active principle and by the pharmaceutical industry in drug-delivery systems to enhance transdermal drug delivery [151].

The evaluation of mixture effects is hampered by a lack of knowledge of the molecular pathways involved along with the large numbers of pollutants and their many potential combinations [152]. Lifetime effects of exposure to chemical combinations are also largely unstudied [111], and may only become evident after people have become sick [132]. Thus, until a risk assessment paradigm is designed for mixture effects, traditional risk assessment tools need to be used with caution when evaluating chemical mixtures [153].

4.3. Timing and Transgenerational Epigenetic Effects

Compelling epidemiological, pharmacological and toxicological evidence shows that there are several vulnerable periods of growth and development. During these periods, environmental interactions with the immune system and genome can increase susceptibility to central nervous system and metabolic diseases later in life [154]. Despite the fact that transgenerational effects arising from poor nutrition and chemical exposures in utero are widely reported in the scientific literature [155–158], the impact of epigenetic factors early in life remains largely unexplored in chemical risk assessment [159]. This is made more poignant by emerging evidence that in utero and early-life exposures may lead to disordered immune responses in adulthood and lead to heritable, epigenetic modifications in the immune responses of subsequent generations [137].

The first association of transgenerational inheritance of disease was documented in the Dutch famine of 1944 to 1945 where nutritional deprivation in utero was associated with increased risks for obesity later in life [160]. Epigenetic inheritance involving environmental chemicals is documented in the daughters of mothers who took the drug diethylstilbestrol (DES) to prevent miscarriages and later went on to have a significantly higher risk of vaginal cancer and other health complaints [161]. Similarly, emerging evidence of transgenerational effects in animal models links autism spectrum disorders to an array of environmental factors such as stress or environmental enrichment, endocrine disruptors such as vinclozolin and BPA, and inadequate nutrition [162].

Whilst the mechanisms by which the effects of exposure are transmitted through the germline to the next generation are still unclear, the most plausible explanation for these associations is the occurrence of epigenetic modifications involving DNA methylation, retained histone modification, tRNA fragments, and non-coding RNAs in somatic and germ cells arising from exposure to various environmental agents during critical windows of development [163]. Genome-wide association studies, in contrast to single nucleotide polymorphisms (SNPs) are likely to provide an important tool to identify the "susceptible biomarkers" to environmental chemicals [100]. The study of gene-environment interactions however, poses special challenges for clinicians because it requires the integration of complex information derived from a comprehensive exposure history, assessment of nutritional status and detoxifications pathways, and genetic profile.

4.4. Individual Factors

There are many individual factors that determine chemical exposure and risk of adverse health outcomes. They include; age, gender, ethnicity, genetics, nutritional status, intestinal microbiota and other lifestyle factors such as diet, smoking, exercise and hobbies, psychosocial determinants and comorbidities [130,132–134], the co- or pre-administration of other drugs, [132,164] and epigenetic

states [165]. Exposure to toxicants also varies widely amongst individuals depending upon: past and current environmental exposures; occupation and health and safety practices; place of residence, work and/or school (proximity to vehicle exhaust, industry, mining, waste sites, industrial accidents, golf courses, parks, farms, flight paths, *etc.*) which is likely to be influenced in part by socioeconomic factors [36]; use of household products, chemicals and pesticides and appropriate use of safety equipment; and access to clean air, water, food and soil.

4.5. New Horizons in Chemical Risk Assessment

Advances in the "omics" fields such as genomics, proteomics and metabolomics, enable the screening of effects of chemical mixtures at the molecular level and the development of more sensitive and specific methodologies for biological monitoring of combined exposures [138,166]. High-resolution metabolomics (HRM) that uses ultra-high resolution mass spectrometry with minimal sample preparation can support high-throughput relative quantification of thousands of environmental, dietary and microbial chemicals and measure metabolites in most endogenous metabolic pathways, thereby providing simultaneous measurement of environmental exposures and their biologic responses [167]. Renewed interest in the placenta as a potential biomarker of exposure and its contributions to long-term human health and disease was recently initiated by the National Institutes of Health: Human Placental Project following evidence of its impact on the health of the mother [168,169] and fetus [170–173]. Prospective follow-up birth cohorts to examine the effects of early life programming will also be important [163]. Emerging technologies are also providing a mechanism to assess the allostatic load at the clinical level. For example, biomolecular adducts formed when a xenobiotic or its metabolite binds to biological molecules (DNA or proteins), are a useful tool to assess exposures to non-persistent chemicals in blood such as organophosphates and aromatic amines before clinical consequences appear [174].

Chemical risk assessment can be vastly improved by gaining better information about the totality of exposures across the life span (exposome) [175]. Prospective, population-based cohort studies have recently started to implement these methods using the exposome framework [166]. Consequently environmental health scientists are exploring new ways to strengthen the integrity of chemical risk assessment using the principles of systematic review [176,177] and some new initiatives are contributing to the refinement and codification of methodological approaches for systematic review and meta-analysis tailored to the specificities of environmental health [178]. To date there have been several attempts at establishing systematic reviews for evaluating data on chemical toxicity [179] including The Navigation Guide [176], the Evidence-Based Toxicology Collaboration [180], the PROMETHEUS project by the European Food Safety Authority [181], Integrated Risk Information System (IRIS) and Tox21 by the joint US EPA, Food and Drug Administration and National Institute of Environmental Health Sciences [182,183], ToxRTool by the European Commission [184], REACH by the European Chemicals Agency and KIimisch Ring Test [185].

Further developments to improve toxicity testing based on animals include a new design from the National Research Council for cellular-response networks that take into consideration advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology thereby allowing scientists to uncover how environmental chemicals may lead to toxicity [134]. Emerging tools like the maximum cumulative ratio will further help to identify a person's cumulative exposure to multiple chemicals over a lifetime [186].

5. The Challenges and Failure of Chemical Regulation

Once an industrial chemical has been tested and its point of departure has been established, it is up to government organisations such as the Environmental Protection Agency, US National Institute for Occupational Safety and Health, Safe Work Australia, European Commission's Scientific Committee on Occupational Exposure Limit Values and non-governmental organisations like the American Conference of Governmental Industrial Hygienists (whose guidelines have been widely

adopted in English speaking countries) to develop ambient air and occupational exposure limits. This process is frequently conducted in consultation with industry, involving scientists employed by various corporations, taking into account what is easily achievable in the workplace [187,188], along with a consideration of economic output and future innovations.

Legislation and the threat of litigation is a powerful motivating force that encourages employers and manufacturers of industrial chemicals to comply with their occupational health and safety requirements. Yet, exposure standards frequently differ from country to country depending upon the approach adopted. In the USA, the "low dose linear extrapolation" approach is favoured and legislated through the Toxic Substance Control Act (TSCA), as opposed to the "margin of exposure" approach used in Europe and regulated through REACH (Registration Evaluation, Authorisation and Restriction of Chemicals) [189]. The stark difference between the two is that REACH is a preventative approach that places the burden of proof on industry to show safety, as opposed to TSCA where the burden of proof is on the government to show harm [130]. As both of these systems primarily focus on industrial chemicals, numerous regulatory authorities have been established to regulate chemicals in food, cosmetics, pesticides and medicinal products. The chemical industry has exploited the inadequacies of weak laws and regulations, inefficient enforcement, regulatory complexity and fragmented overlapping authorities, to enable the introduction of untested chemicals into the commercial products and the environment [111,190]. Furthermore, non-occupational exposure standards for indoor air quality in residential environments are lacking, despite organisations such as the World Health Organisation [191] and the US Environmental Protection Agency [192] producing numerous reports and guidelines on indoor air quality.

The wide variation in exposure standards across jurisdictions along with vast numbers of commercial chemicals in widespread use that have not been adequately assessed for neurodevelopmental toxicity, endocrine disruption or other toxic effects, points to inadequacies in current chemical risk assessment procedures. Such inadequacies were highlighted as early as the 1970s by Bruce Ames who subsequently developed the Ames test for assessing the mutagenic potential of chemical compounds [193]. More recently, existing chemical risk assessment practices have come under scrutiny from various governmental and non-governmental bodies including the US Environmental Protection Agency [194], National Resource Defence Council [190], European Union (who responded by developing REACH), the National Academy of Sciences and the Institute of Medicine [130] and medical organisations such as the American Medical Association [195] and the American Academy of Paediatrics [196].

The availability of scientific information is fundamental to the ability to understand and manage risk and form the basis for regulatory action. However, while compelling epidemiological, animal and *in vitro* evidence is required to prove harm from a chemical exposure [111], there is a lack of well-accepted tools to objectively, efficiently and systematically assess the quality of published toxicological studies [197] making it difficult to assess health risks associated with low level exposure to hundreds of chemicals over a life time. Thus, for almost every conclusion about chemical-related health risks, it is possible to find a dissenting view [179] and the vast majority of scientific reviews conclude that "more research is needed".

6. What Are the Barriers for Chemical Assessment in Clinical Practice?

While chemical risk assessment requires the application of multiple scientific fields to public health and regulatory issues, it is up to individual clinicians to determine the relevance of the many issues involved to the current and future health needs of their individual patients. Environmental chemical assessment in clinical practice therefore requires the personalization of medicine using the translation of a complex knowledge base to determine an individual's body burden of toxicants, along with their personal risk factors and health status. Yet, despite the many scientific developments occurring in the area of chemical risk assessment, the discrepancies amongst leading authorities in their interpretation for evidence of harm makes it difficult for clinicians to translate scientific information into clinical

practice. Furthermore, while clinicians must deal with the consequences of environmental chemical exposures and remain one of the most often accessed and most trusted sources of information about the health and the environment [198], there is widespread agreement that clinicians lack adequate information and training with respect to environmental risks and health [199,200].

6.1. What is Environmental Medicine?

A lack of clinical training in environmental medicine may be partly due to inconsistencies in defining "environmental medicine" and the confusion as to where it fits in relation to other specialties such as public health and occupational medicine. In the mainstream scientific literature, environmental medicine is defined as the evaluation, management, and study of detectable human disease or adverse health outcomes from exposure to external physical, chemical, and biologic factors in the general environment [199,201]. This is in contrast to occupational clinicians whose definition of environmental medicine varies depending upon the country and include: "exposures arising from industrial activities at a workplace" (Australia), "embracing any influences on health and disease that are not genetic" (UK), or as "a branch of medical science which addresses the impact of chemical or physical stressors on the individual or group in a community" (USA) [202]. To add to the confusion, public health clinicians define environmental medicine more broadly as "issues in the physical environment which impact on health, encompassing quality of air, water and food" [202]. Consequently environmental medicine has become a specialty field under the guise of "occupational and/or environmental medicine" and "public health" with the majority of "environmental physicians" focusing on public health issues rather than patient-centered clinical practice [203]. Wide inconsistencies in the definition for the term "environment", has further ramifications for establishing environmentally attributable risk estimates. For example researchers and publications that define the environment in the narrow sense (air, water, food, and soil pollutants) tend to have smaller attributable risk estimates, whereas researchers and publications that refer to the environment in the broadest sense (including lifestyle factors, occupational exposures, and pollutants) have consistently larger risk estimates [106].

Relegating environmental health to a specialty field is highly problematic when environmental chemical exposures are implicated in many of the conditions seen by clinicians on a daily basis, yet the tools and expertise to adequately assess or manage these exposures are not widely available [200]. Furthermore, few doctors take adequate occupational or exposure histories [204] or refer patients to environmental physicians [123] and therefore environmental exposures are seldom identified in disease causation [111]. Consequently the cadre of environmental oncologists, researchers and clinicians trained in environmental health are relatively small, which may explain why environmental health is largely excluded from national policy [111].

6.2. Medical Training

There is a widely acknowledged need for greater awareness about chemical assessment amongst clinicians. The need for general clinicians to familiarise themselves with the health impacts of environmental chemical exposures was highlighted in 1967 at a conference by the American Medical Association's National Congress on Environmental Health Management, and was further highlighted by the American College of Clinicians [205,206] as well as being a focus of the International Federation of Environmental Health in 1991 [207] and 2013 [208]. Despite the recognized need for clinical education on environmental chemicals, there appears to be a severe lack of environmental health education in medical undergraduate curricula. The Institute of Medicine has been particularly vocal about the lack of environmental health training as evidenced by the publication of the book "Role of the Primary Care Physician in Occupational and Environmental Medicine" [200], and the report "Environmental Medicine—Integrating a Missing Element into Medical Education" [199], which outlined a six competency-based learning objectives for medical students. This is further reinforced by the World Health Organisation's report "Environmental Health and the Role of Medical

Professionals" [209], which highlights the medical professionals role in assessing, investigating, diagnosing, monitoring, treating and preventing environmentally-related disorders.

The lack of environmental education for clinicians can be seen to be due to competition from other disciplines in crowded medical curricula, lack of funding and a lack of appropriately trained academics [210]. A significant proportion of undergraduate medical training is devoted to pharmacology as opposed to toxicology [211] or environmental health, with the exception of medical toxicology, a specialty field involving acute high dose exposures confined to emergency clinicians [212]. Furthermore, nutrition is rarely taught in undergraduate medical training despite the fact that the nutritional state of the person affects the impact and metabolism of toxicants in key Phase 1 and 2 metabolic detoxification pathways [132]. Not surprisingly, a recent survey of medical school graduates found that more than one-third of respondents said they received "inadequate" instruction in environmental health [213].

Both the World Health Organisation [214] and the American Academy of Paediatrics [27] acknowledge the lack of training in medical schools, and recommend that children's environmental health be incorporated into the training for health care providers. Others have noted that obstetricians and gynaecologists are well positioned to prevent hazardous exposures in light of the irreversible impacts on health arising from chemical exposures in utero [215]. Aside from nutrition, smoking and drinking during pregnancy, obstetrics-gynecology education has been largely void of environmental health [216]. A recent report by the International Federation of Gynecology and Obstetrics recommended that reproductive and other health professionals advocate for policies to prevent exposure to toxic environmental chemicals, work to ensure a healthy food system for all, make environmental health part of health care, and champion environmental justice [85]. Calls to action are starting to be heard with the Association of American Medical Colleges recent webinar on "Teaching Population Health: Innovative Medical School Curricula on Environmental Health" [217] outlining the need to educate undergraduate medical students in environmental health which included links to the American College of Medical Toxicology's Environmental Medicine Modules [218].

6.3. Environmental Health Data and Its Relevance to Clinical Practice

The sheer number of scientific journals, non-governmental organisations, associations, professional societies, environmental medicine practitioner organisations and governmental agencies dedicated to environmental health is enough to leave clinicians overwhelmed and despondent in ever gaining a grasp of this complex and ever growing field. The number of journals dedicated to public, environmental and occupational health under the category "Clinical Medicine" in the Web of Science database grew from 101 in 2005 to 142 in 2010 yet very little of the vast amount of literature on environmental health is actually published in general medical journals. This is likely to be due to a variety of factors. Firstly, evidence about environmental exposures based on animal studies in the absence of human experimental data is considered "weak evidence" by the medical fraternity and outside the comfort zone and time constraints of most clinicians [219]. In addition, whilst epidemiological studies are important tools for determining risk, they can be limited by often failing to take into account the role of individual differences reflected in subpopulations [220]. For much of the history of clinical trials, the treatments under investigation were assumed to apply to anyone with the relevant clinically defined condition [221]. However the emerging "omics" fields and molecular cancer epidemiology, has led to the recognition that clinical trials need to be redesigned to account for individual variations ($N = 1$) arising from one's genomic profile, lifestyle and environmental exposures.

How do we accommodate evidence in the context of individual patients? As it is not viable to devote resources to generate randomised clinical data on patients whose variants are so unique that they represent a small minority of the community, a shift is needed in the way we think about evidence-based medicine. Despite rapid advances in technology and the volume of literature published about the adverse health effects arising from exposure to environmental chemicals, health care systems

have fallen far short in their ability to translate knowledge into practice and to apply new technology safely and appropriately [222].

7. How Can Clinicians Assess Environmental Chemical Exposures?

Whilst biomonitoring is an established approach to evaluate the internal body burden of environmental exposures, the use of biomonitoring for exposome research is limited by the high costs associated with quantification of individual chemicals [167]. Interpretation of the presence of chemicals in human tissues has also been the subject of much controversy, as its presence cannot be taken to imply that there will be adverse functional consequences [123,223]. For example blood and urine samples generally only reflect recent exposures to toxicants (heavy metals, persistent organic chemicals, organophosphate (OPs) and carbamate pesticides); hair and nails reflect past exposures (pesticides, heavy metals, polychlorinated biphenyls and polyaromatic hydrocarbons), are easily contaminated and difficult to collect in a standardized way; and many other biological matrices such as human milk, saliva, adipose tissue and meconium lack reliable reference values for human populations [138].

Resources and tools to educate clinicians and elicit personal environmental health data in the clinical setting are limited in scope and applicability. For example, the Australian NHMRC 2011 Standard for Clinical Practice Guidelines portal does not provide any guidelines on how to assess environmental chemical exposures, despite the fact there are extensive guidelines for conditions like diabetes, which are known to be influenced by chemical exposures. The lack of guidelines is compounded by a lack of conventional pathology tests to assess environmental chemical exposures. In addition, the knowledge required to understand what, how and when to assess environmental chemical exposures requires extensive knowledge on individual toxicants, their metabolites and/or the product of toxicant interactions with endogenous targets [174], which is not generally considered within the realm of most clinicians.

Tools that are available such as the EPA's Office of Pesticide Protection questionnaire, the CDC's Agency for Toxic Substance and Disease Registry "Taking an Exposure History Guide", The Navigation Guide, Eco-Health Footprint Guide (Global Health and Safety Initiative), Quick Environmental Exposure and Sensitivity Inventory (QEESI), WHO Paediatric Environmental History to name but a few, are unlikely to be known by most general clinicians, and have either not been validated and/or require lengthy periods of time to complete, which may not always be practical in a clinical setting. Consequently clinicians and those specialising in idiopathic multimorbidity, are likely to have developed their own assessment procedures to assess their patient's susceptibility or exposure to environmental toxicants. Such procedures may include extensive historical inquiries (paediatric, occupational and environmental exposure histories) along with an assessment of their patients' metabolic, nutritional, genetic, and exposure profiles and include unconventional tests performed at pathology laboratories from around the globe such as Acumen Labs, Nutripath, Doctors Data, Genova Diagnostics, Healthscope Functional Pathology, Mycometrics, US Biotek Laboratories, Great Plains Laboratory and AsureQuality Labs, amongst others. Such assessments may come at considerable expense to their patients and as exposure standards are not available for many biomarkers, these clinicians must interpret the data without the benefit of published normal ranges or specific diagnostic criteria.

To assess environmental chemical exposures in patients, the challenge for clinicians is to ask relevant questions to elicit toxicant sources and exposure, identify the most relevant tests and to digest data from multiple streams (traditional medical data, "omics" data and quantified self-data), and place this information in the context of individual patients in a way that has measurable and meaningful outcomes. Only by doing so, can medicine shift the focus from treating disease, to prevention and wellness.

7.1. Lessons in History—Asking the Right Questions

The history of medical care is littered with examples of missed opportunities, wasted resources and counter-productive policies, due to the inability to effectively assemble and act on available evidence on toxicant exposure [179]. Environmental tobacco smoke, asbestos, lead dust, benzene, polychlorinated biphenyls, chlorofluorocarbons, lead and organochlorine pesticides are just some examples where warnings were ignored decades prior to the emergence of devastating public health issues [224]. History also provides examples of doctors whose observations at the clinical level, in addition to the power of rapid action, resulted in significant improvements in public health. For example, in the 18th century, British surgeon, Sir Percivall Pott, without knowing the cause or mechanism of action, stopped an epidemic of scrotal cancer in chimney sweeps by asking them to improve their genital hygiene [225]. Furthermore, in 1854, Dr. John Snow who is credited as the first epidemiologist, was able to prevent an outbreak of cholera by dismantling a water pump handle in Broad St, London, despite great criticism from his peers [226].

7.2. The "Omics" Revolution and Personalised Medicine: A Match Made in Heaven

Following completion of the Human Genome Project in 2003 in conjunction with the rapid advances in bioinformatics, the "omics" fields exploded onto the scene, challenging our understanding of the nature and cause of disease, whilst also shifting the focus to what it means to be well. Clinical genetic testing has transformed from being centred on mutation detection for Mendelian disorders like sickle cell disease to personal genomic data as a way to predict ancestry and assess disease risk. The emergence of hand-held devices such as the "SNIP doctor" for analysing single nucleotide polymorphisms, has bridged the gap from the bench to the bedside [227]. Whilst the brunt of these discoveries has yet to infiltrate clinical practice (because it takes an average of 17 years to incorporate scientific discovery into clinical practice [222]), the ramifications of these findings will provide more precise treatment for individuals and issue a new era in personalised medicine.

Breast cancer risk provides a good example. Whilst the aetiology of breast cancer is still not fully understood, there are several known risk factors including: the age of menarche/parity/menopause; family history of breast cancer; length of time of breast feeding; body mass index; drugs (hormone replacement therapy, oral contraceptive pill); exercise; alcohol intake; and cigarette smoking [228,229]. Given that the prevalence of gene mutations (BRCA1, BRCA2) for women diagnosed with breast cancer are low (5.3% and 3.6% respectively) [230], it has been suggested that low-penetrance susceptibility genes combined with environmental factors may be important risk factors [231]. Advances in genomics have identified several gene variants (single nucleotide polymorphisms (SNPs)) in key detoxification pathways that maybe associated with breast cancer susceptibility [232–236]. However few of these variants (COMT, CYP1B1, GSTP1, MnSOD, MTHFR) have been shown to contribute to breast cancer risk individually except when these polymorphisms are combined [237], or in the presence of relevant environmental chemical and lifestyle exposures [238,239]. This is significant in light of the fact that unique populations of various ethnicity have been shown to have polymorphic variants in detoxification enzymes, which may predispose them to increased adverse health effects from environmental chemical exposures [240,241]. For example, despite the low incidence of breast cancer amongst Asian women [242], a recent meta-analysis to determine the role of MTHFR C677T polymorphism in breast cancer risk, showed a strong significant association between TT genotype and breast cancer which is far more prevalent in the Asian population compared with the Caucasian population [235]. This may explain why US-born Asian women have an almost two fold higher incidence of invasive breast cancer than foreign-born Asian women [243], implying that epigenetic effects involving lifestyle, dietary, and/or environmental factors are likely to play a role. The results of these findings, may explain why so many risk factors have been implicated in breast cancer and other chronic diseases, and yet a causal relationship has not been definitively established.

As stated by Dr. Francis Collins, Director of the US National Institutes of Health "*genetics loads the gun and the environment pulls the trigger*". Thus establishing an individual's risk to environmental

chemicals based on the presence of low penetrance genes (SNPs) alone is limited unless it is combined with the potential epigenetic effects of pathological, developmental, dietary and environmental chemical exposure history across the lifespan [244]. The concept that the phenotype is the consequence of gene-environment interaction was highlighted by Archibald Garrod in 1902 who suggested that individual differences in genetics could play a role in variation in response to drugs, and that this effect could be further modified by the diet [245]. However, while genetic testing is providing greater understanding of disease risk, the application of gene testing at the clinical level is fraught with challenges.

Very few of the one million plus SNPs identified in genome wide association studies have clear functional implications and actionable outcomes that are relevant to mechanisms of disease [246], which is why clinicians perceive the analysis of genetic data as requiring considerably more time and work with uncertain outcomes [247]. Secondly clinical guidelines for genomic testing is still in its infancy, such that there is a poor understanding of the effect of individual alleles, many of which appear to be non-sense mutations but may at a later date prove to be of clinical relevance especially in the context of other alleles, epialleles and environmental exposures [248]. Furthermore, the accuracy of laboratory analysis of genetic information and interpretation of results may vary amongst direct-to-consumer genetic testing companies depending upon their quality control standards [249]. Despite the remarkable advances in biomedical research and in particular, the field of genomics in the past twenty years, concerns have been raised about the lack of knowledge and skills in genetic and genomic testing, interpretation of test results, communication of results to patients and families, and basic genetic counseling amongst general non-academic clinicians [250,251]. Finally and perhaps most importantly, clinical genomics requires an understanding of the ethical, legal and social considerations associated with genomic profiling including employment and health insurance nondiscrimination, patient's rights, informed consent, disclosure, microarray screening for pregnancy, cost/benefit ratio, drawbacks *versus* perceived benefits, genetic counselling, protection of privacy and data protection [252–254]. Clinicians will therefore need educational programs that target relevant scientific, clinical, ethical, legal, and social topics and support systems that address structural and systemic barriers to the integration of genetic medicine into clinical practice [251].

7.3. Citizen Science and Mobile Technologies

It is clear that the impact of environmental chemical exposures is an issue that requires action at many levels and must ultimately include the general community. Thus, civil society, including non-government organisations and civilian advocates can play a vital role in shedding light on the nature and extent of chemical exposures and their impacts. As such, citizen science or "participatory urbanism" is an emerging field that shows great promise in the scope of environmental awareness and regulation [255]. This became evident as early as the 1960s when a citizen science project revealed widespread contamination from radioactive fallout from atomic weapon testing through the analysis of strontium 90 in baby teeth collected from around the world, leading to the signing of the Partial Nuclear Test Ban Treaty in 1963 [256].

The potential for participatory citizen science has expanded enormously since the 1960s. Consumer's appetite for health information is evident by the 40,000+ smartphone health applications now available [257] and the fact that almost 60% of mobile phone users have downloaded a health app [258]. Furthermore, genomic profiling is now available for as little as $99 from companies like 23andMe who have databases in excess of one million clients. With more tools at their disposal, web applications have enabled citizens to take a proactive approach to make informed health-care decisions. No longer passive recipients of health care, these "e-patients" have given birth to the quantified self-movement, and irrevocably changed the traditional doctor-patient relationship making way for the participatory medical model. Furthermore, the advent of the internet along with rapid advances in mobile computing, wearable devices, nano-biosensors, lab on a chip technology, geographical information systems, the quantified-self movement, the internet of things, big data analytics and cloud

computing, represent disruptive innovations that promise to create a fundamental shift in biological discovery. Such advances, which enable the real-time measurement of physiological and psychological states along with environmental measures, offer the ability to better predict, detect and prevent disease brought on by chemical exposures and thus radically accelerate our understanding of the health impact of environmental chemical exposures [259].

Widespread adoption of information technology applications requires behavioral adaptations on the part of clinicians, organizations, and patients [222] and the ability of technology designers to build better tools and platforms that allow patients to share data with their doctors in order to augment existing medical knowledge and practices [247]. Whilst citizen science has the potential to build important bridges between scientists, clinicians and the public with positive outcomes for all [260], clinicians need to be receptive to the shift in the availability of knowledge to the public and be capable of answering questions that might arise so they can direct patients to credible and reliable resources when appropriate [261]. Engaging volunteers in rigorous science, global-scale citizen science projects also provide an excellent opportunity to promote awareness, and educate and empower individuals and clinicians to find solutions to problems that would otherwise be large and overwhelming [260].

While citizen science and mobile technology has the potential to engage the wider community in monitoring and reducing exposures to environmental pollutants, currently there is a lack of integration between data sources and a key challenge is the integration of big health data streams. Incorporating "big data" arising from traditional medical data, "omics" data and quantified self-data to routine clinical care will be a formidable and challenging task, and yet one that is vital for the emergence of personalised medicine that is predictive, personalised, preventative and participatory (4Ps). This challenge has been taken up by the field of systems biology, which uses computational mathematical tools that promise to unify multiple data sets—personal, clinical, genomic, geographical and environmental data. Systems biology therefore provides the foundation for personalised medicine where the patient becomes an integral part of the identification and modification of disease related risk factors and the clinical decision-making processes takes advantage of the most up-to-date scientific knowledge [262].

7.4. Tomorrow's Doctor

The failure of regulatory authorities to manage risk associated with environmental chemicals, in addition to the widespread and growing number of chemicals found in the human population, provides clinicians with unique and important roles to play in identifying and preventing environmental chemical exposures. While there some clinicians who are supported by integrative/functional medicine associations that are rising to meet this challenge, there are no standard practice models and these clinicians have had to engage in continual education, develop their own clinical assessment tools, and navigate a path through the complex landscape of laboratory tests and the emerging science in multiple fields. This is an extremely challenging task, as conducting environmental chemical assessment at the clinical level includes (but is not limited to):

- Establishing the patient's inherent susceptibility to environmental chemicals through assessment of their demographics, ethnicity, socioeconomic status, comorbidities, nutritional and genomic profile.
- A detailed place history that includes places of residence and work across the lifespan and throughout the week including primary modes of transportation and an assessment of the patients living conditions including their proximity to traffic and other sources of air pollution and potential sources of lead and other heavy metals, mould, dust, indoor air pollution and chemicals in building materials, furnishing and consumer products.
- An obstetric, paediatric, environmental and occupational exposure history that includes a detailed dietary history, drinking water sources, pharmaceutical and recreational drug use and general lifestyle factors including the use of chemicals in the home and garden, cooking utensils, cleaning methods, personal care products and consumer goods.

- A family history that includes previous generations.
- A detailed symptom history that includes a timeline from the perinatal period and enquiry into multiple organ systems.
- A physical examination to look for physical signs of metabolic, neurological, reproductive or other disease and co-morbidities.
- Assessing current toxic load through performing various biomonitoring tests that include assessment of biomarkers in various body tissues to assess long term accumulation of toxicants as well as short term exposures.
- A consideration of external data sources such as geographical information systems and governmental or non-government environmental pollution reporting, ambient air monitoring, drinking water quality and any crowd-sourced data.
- Networking with other professionals who can assess the patient's home and/or workplace to establish sources of exposure.
- Keeping up with the latest regulations and scientific information on environmental chemicals and how they may be assessed as well as their interactions with each other, different diseases and individual patient factors.

To achieve this, clinicians need to possess a cluster of related knowledge, skills and attitudes in the fields of genomics, nutrigenomics, microbiology, hygiene, toxicology, occupational health, public health, epidemiology and, from a clinical perspective, nearly all fields, as well as general medicine, paediatrics and oncology. In addition to clinicians dedicating themselves to this task, the politics and economics of contemporary medicine need to support the dissemination and implementation of this kind of information. However there are many obstacles that hinder this process including the complexities involved in integrating data from numerous emerging fields, time constraints imposed on clinicians, educational requirements, the need for population and individual biomonitoring, the lack of clinical assessment tools, pathology facilities and adequate risk based regulation, profit based funding models that favor treatment over prevention, and the lack of political will to implement drastic changes in how we produce, monitor and regulate chemicals. Ultimately the issues raised by environmental chemical exposures are far greater than those that can be faced by clinicians, as they affect all people and indeed all life on earth. There is a need therefore for concerted action at all levels including actions by individual patients, clinicians, medical educators, regulators, government and non-government organisations, corporations and the wider civil society in order to understand and minimise the extent of toxic exposures on current and future generations.

8. Conclusions

Large population biomonitoring studies have revealed widespread exposures to environmental chemicals at levels in humans known to cause adverse health effects. Despite emerging evidence associating many of these chemicals with chronic diseases typically seen in general clinical practice, environmental chemical assessment has largely been overlooked in clinical practice. Part of the reason lies in the scientific complexities involved, inadequacies in chemical regulations and chemical risk assessment, inconsistencies in defining environmental medicine, a lack of information on environmental chemicals in general medical journals, inadequate pre- and post-graduate medical education on environmental medicine, the limitations of current biomarkers and laboratory tests, along with time, funding and political constraints that limit the use of available tests in clinical practice.

Assessing environmental chemicals in clinical practice may very well be the toughest challenge facing medicine today. Determining susceptibility to environmental chemicals requires a sophisticated understanding of each individual patient and the use of increasingly refined approaches that incorporate extensive paediatric, environmental, geographical, occupational and lifestyle data. The clinical assessment of environmental chemicals also involves embracing the gene-environment paradigm and moving beyond reactive disease models to one that is proactive and preventative,

whilst also acknowledging the vital role patients play in their own wellbeing. Recent developments in the fields of systems biology, and the "-omics" fields and advances in peer-to-peer wireless sensor networks, may soon offer tools that provide a bridge between multiple disciplines and herald a new era in personalised medicine that unites clinicians, patients and civil society in the quest to understand and master the links between the environment and human health.

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