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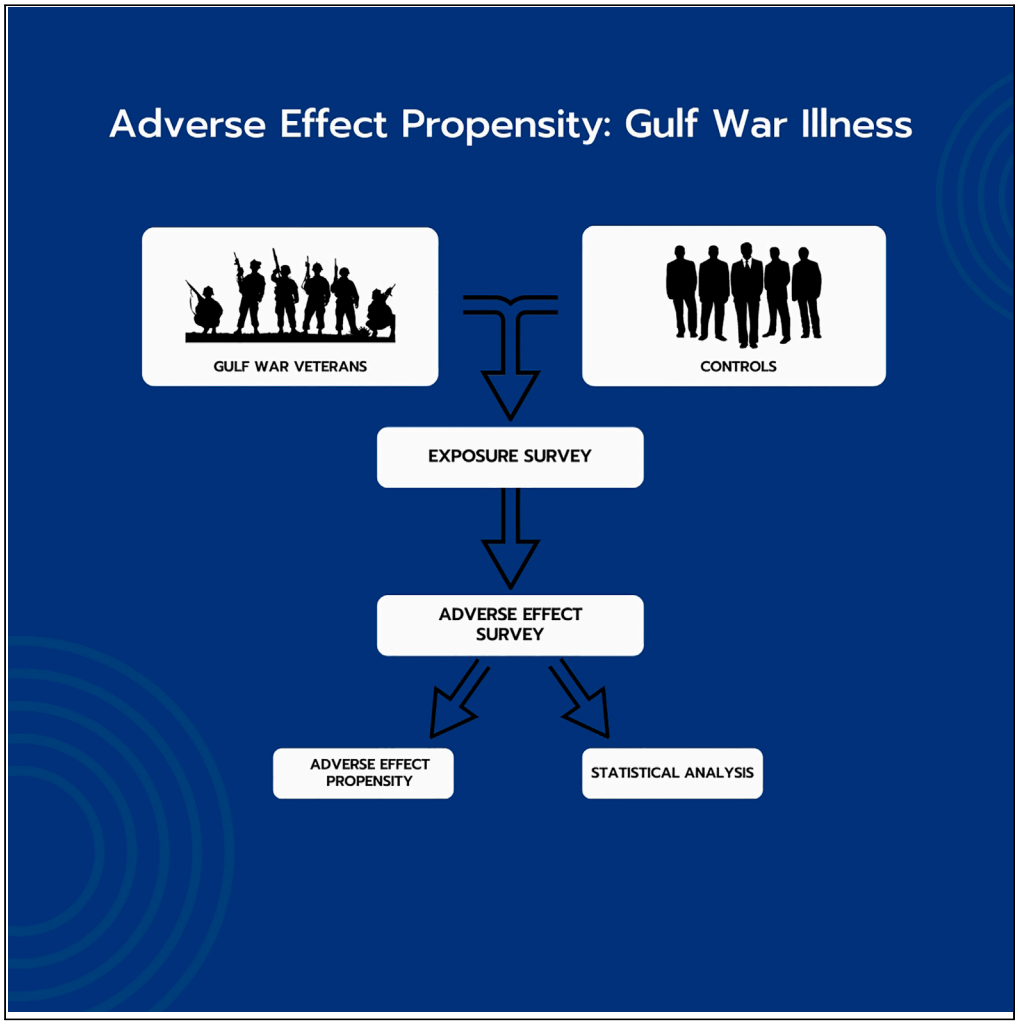

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Highlights

Some people experience adverse effects (AEs) to many drugs/chemicals of differing class

Total AE Propensity (TAEP) was greater in veterans with Gulf War illness (VGWI)

Pesticides and radiation predicted greater TAEP, while copper appeared protective

Exposures reproducibly predicted TAEP in all, VGWI, controls, and age strata

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Adverse effect propensity: A new feature of Gulf War illness predicted by environmental exposures

Beatrice A. Golomb[1,2,*] and Jun Hee Han[1]

SUMMARY

A third of 1990-1 Gulf-deployed personnel developed drug/chemical-induced multisymptom illness, "Gulf War illness" (GWI). Veterans with GWI (VGWI) report increased drug/exposure adverse effects (AEs). Using previously collected data from a case-control study, we evaluated whether the fraction of exposures that engendered AEs ("AE Propensity") is increased in VGWI (it was); whether AE Propensity is related to self-rated "chemical sensitivity" (it did); and whether specific exposures "predicted" AE Propensity (they did). Pesticides and radiation exposure were significant predictors, with copper significantly "protective"—in the total sample (adjusted for GWI-status) and separately in VGWI and controls, on multivariable regression. Mitochondrial impairment and oxidative stress (OS) underlie AEs from many exposures irrespective of nominal specific mechanism. We hypothesize that mitochondrial toxicity and interrelated OS from pesticides and radiation position people on the steep part of the curve of mitochondrial impairment and OS versus symptom/biological disruption, amplifying impact of new exposures. Copper, meanwhile, is involved in critical OS detoxification processes.

INTRODUCTION

Gulf War illness (**GWI**) is a chronic multisymptom illness affecting approximately one-third of the ~700,000 U.S. troops deployed to the 1990-1 Persian Gulf theater of operations.[1,2] It is a symptom-characterized condition, typified by multiple symptoms spanning protean domains, including fatigue/sleep, pain, neurological, respiratory, gastrointestinal, dermatological, and autonomic.[3] Numerous objective markers have been found to be altered in GWI,[4–7] though there is no pathognomonic test. Alterations with replicated documentation include increased inflammation,[8,9] mitochondrial impairment,[6,10–12] altered eicosanoids,[4] altered hormone status,[13,14] altered autonomic function,[7,15,16] and increased autoantibodies[5,17,18]—among others.

Veterans with GWI (**VGWI**) have repeatedly been found to be at increased risk of developing multiple chemical sensitivity (**MCS**).[3,19–24] Many also report intolerance to numerous medications and some cite intolerance to electromagnetic radiation (**EMR**).[25] In a recent meeting of the Department of Veterans' Affairs Research Advisory Committee on Gulf War Veterans' Illnesses,[26] in the "Public Comment" session, a veteran inquired whether/what additional work was being done on chemical sensitivity in VGWI.

Adverse effects (**AE**s) of many drugs, chemicals, and radiation involve intertwined mechanisms of oxidative stress and mitochondrial impairment—irrespective of the nominal specific mechanism of action of the agent (or frequency of the radiation).[27–43] MCS, nonionizing radiation sensitivity, and ionizing radiation sensitivity involve oxidative and mitochondrial mechanisms.[44–49] Thus, a relationship between propensity to experience AEs to environmental factors, including radiation, and self-reported chemical sensitivity is plausible. Since mitochondrial injury may lead to ongoing oxidative stress/free radical production,[50–52] leading to increased competition for antioxidant defenses—and positioning mitochondrial injury further along the path toward clinical mitochondrial "threshold effects"[53,54] that may be triggered by a new exposure, it is plausible that specific past exposures may have contributed to enhanced risk of AE vulnerability in VGWI.

The UCSD Gulf War illness study is an observational study that has produced findings on Gulf War illness relations to metabolomics, prostaglandins and leukotrienes, malondialdehyde, citric acid cycle markers, and the vaccine experience.[4,12,55,56] Data from that study were here used to examine two questions: first, have VGWI indeed manifested increased apparent vulnerability to AEs of exposures received (case-control

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analysis). Second, to what extent are specific exposures associated with vulnerability to AEs spanning exposures to many drugs and chemicals—and how does this AE Propensity relate to self-rated chemical sensitivity (cross-sectional analysis). This was not prespecified but considering the challenges to study participation for this compromised group, we consider there to be an ethical desideratum to glean the greatest possible information from the sacrifices made by veterans to participate; and to accelerate science and hypothesis generation related to concerns of this group, while VGWI remain alive to potentially benefit from the knowledge gained.

RESULTS

Participants: The study involved a one-time visit. Because there was only one visit, no dropouts between visits occurred. All eligible/interested qualifying cases and matching eligible/interested controls were seen and evaluated, and all eligible parties included in analysis. One extra case was recruited to expand demographic options for identifying a matching control. However, for this study, all participants, including the "extra" (unmatched) case, are included in the analysis.

As Table 1 shows, GWI cases and controls were (by selection) closely similar on age, sex, and ethnicity. VGWI were more likely to be married, perhaps reflecting that for those with this condition, those who have social support are more likely to be able to add research study participation to their challenging lives.

Table 1 also shows symptom scores based on Kansas criteria, for all, and for cases and controls separately. Different numbers of symptom queries are asked for the different domains, providing large differences in maximum possible score, and accounting for material differences in mean scores across domains, in all, in GWI cases, and in controls. The mean summed symptom score for affected veterans is almost 40, and is approximately 75 times higher than the mean score for controls. (Cases are selected for/defined by the presence of symptoms in these categories, as described previously; while controls are selected for a dearth of such symptoms.)

The focus of our analysis was on reported AEs, rather than whether participants considered themselves to be chemically sensitive. However, some data are available for the latter. Table 1 shows self-rated chemical sensitivity, based on a Kansas criteria question and our own question.

"chemsenssx" was assessed as a binary (and also as an ordinal variable) variable, "chemsensbinary", rated 1 if the chemsenssx variable was rated 1, 2, or 3; and 0 if it was rated 0. These variables cannot be assessed against individual exposures in controls (because only one control reported chemical sensitivity), a further impetus to focus on predictors of actual AE Propensity.

Table 1 further shows the summed AE score, the summed exposure score, and the ratio of the summed AE score to the summed exposure score—the total AE Propensity—in all, in cases and in controls. Affected Gulf War veterans' summed exposure scores were about 4 times higher, while summed AE scores were close to 10 times higher than controls' scores. AE Propensity was approximately three times higher in GWI cases than in controls.

A key purpose of this study is to examine whether there is a relationship between nature of exposures experienced and propensity to develop AEs.

To maximize prediction in multivariable models, while limiting the number of included variables, composite variables were generated by summing potentially important exposures within a class. The pesticide variable included pesticides on clothes or bedding and pyrethroids. The composite fuel-fume variable included burning fuel, diesel fumes, diesel on skin, petroleum products, degreasers, and carbon monoxide. (The relation of diesel fumes to carbon monoxide and carbon monoxide to fume exposures may be difficult to disentangle, so these were included in a single variable.) A composite radiation variable included radiation therapy, X-ray radiation, radioactive chemicals, and other radiation. Table 1 shows the mean values of these variables in all, in cases and controls, and the case-control difference. Mean values and ranges assist in interpreting coefficients in regression.

Total AE Propensity showed modest relationships to Kansas domains with the strongest relationship being to skin symptoms in cases and to gastrointestinal (**GI**) symptoms in controls (Table 2).

Table 1. Participant characteristics

	N	All N = 81 Mean (SD)[a]	Case N = 41 Mean (SD)	Control N = 40 Mean (SD)	p case vs. control
Age (Years)	81	49.8 (7.5)	50.1 (7.6)	49.5 (7.5)	0.68
Male %	81	92.6	92.7	92.5	0.98
Ethnicity %	81				
Caucasian		54.3	53.7	55.0	0.90
African American		21.0	22.0	20.0	0.83
Latino		14.8	14.6	15.0	0.96
Asian		7.41	7.32	7.50	0.98
Native American		2.47	2.44	2.50	0.99
Married %	81	53.1	65.9	40.0	0.020
Kansas symptom subscales	81				
Total fatigue		3.88 (4.33)	7.49 (3.20)	0.175 (0.501)	**<0.0001**
Total pain		2.73 (3.14)	5.27 (2.48)	0.125 (0.404)	**<0.0001**
Total neurological		9.47 (11.0)	18.5 (8.31)	0.175 (0.501)	**<0.0001**
Total skin		0.95 (1.67)	1.85 (1.96)	0.025 (0.158)	**<0.0001**
Total GI		1.86 (2.44)	3.66 (2.29)	0.025 (0.158)	**<0.0001**
Total respiratory		1.19 (1.85)	2.32 (2.04)	0.025 (0.158)	**<0.0001**
Total Kansas symptoms		20.1 (22.5)	39.1 (16.1)	0.550 (0.959)	**<0.0001**
Chemsensk (0–3)	81	0.593 (0.946)	1.15 (1.06)	0.025 (0.158)	**<0.0001**
Rated 0, 1, 2, 3		*54, 11, 11, 5*	*15, 10, 11, 5*	*39, 1, 0, 0*	***<0.001***
Chemsenssx	80	0.575 (1.02)	1.13 (1.20)	0.025 (0.158)	**<0.0001**
Rated 0, 1, 2, 3		*57, 8, 7, 8*	*18, 7, 7, 8*	*39, 1, 0, 0*	***< 0.001***
Chemsensbinary	81	0.284 (0.454)	0.537 (0.505)	0.025 (0.158)	**<0.0001**
Rated 0, 1		*58, 23*	*19, 22*	*39, 1*	***< 0.001***
totAE: Summed AE score	81	12.0 (14.9)	21.4 (14.8)	2.31 (6.33)	**<0.0001**
totExp: Summed exposure score	81	38.4 (28.7)	60.9 (21.5)	15.4 (12.0)	**<0.0001**
AE Propensity[b]	81	0.216 (0.209)	0.330 (0.172)	0.100 (0.176)	**<0.0001**
Composite pesticide	81	0.51 (0.72), 0-2	0.90 (0.75)	0.10 (0.38)	**<0.0001**
Composite fuel	81	2.00 (2.02), 0-6	3.20 (1.82)	0.78 (1.39)	**<0.0001**
Total radiation	81	1.78 (2.03), 0-8	2.60 (2.27)	0.95 (1.32)	**0.0002**

GI = gastrointestinal. chemsensbinary = a binarized version of chemsenssx (The missing value for chemsenssx was assigned a value of 0.). chemsensk = having physical or mental symptoms after breathing in certain smells or chemicals. chemsenssx = chemical sensitivity (e.g., unusual sensitivity to smells). AE = adverse effect. totAE = summed adverse effect score. totExp = summed exposure score. Composite pesticide: sum of pesticides on clothes or bedding, and pyrethroids. Composite fuel: sum of burning fuel, diesel fumes, diesel on skin, petroleum products, degreasers, and carbon monoxide. Total radiation: sum of radiation therapy, X-ray radiation, radioactive chemicals, other radiation, SD = standard deviation. N = number. p = probability (two-sided).

[a]Except where "%" is signified in characteristics column.

[b]Summed AE score/summed exposure score.

Table 3 shows the relation of AE Propensity to self-rated chemical sensitivity, by the various measures, in GWI cases. (This is not meaningful in controls, with only one participant designating themself as chemically sensitive.) The strongest relation of AE Propensity is to the UCSD binary chemical sensitivity measure. This analysis uses correlation, which though not the optimal assessment when a variable is binary, provides a more intuitive index of the relationship, for comparison across measures. This affirms that AE Propensity is related to self-rated chemical sensitivity but is not isomorphic to it.

On a similar theme, Table 4 shows the mean AE Propensity, by chemical sensitivity rating, for the two binary ratings and for the Kansas rating. Those who consider themselves to be chemically sensitive, on average

Table 2. Relation of AE propensity to Kansas GWI symptom domains

	All		Cases		Controls	
Kansas domain	*r*	*p*	r	p	r	p
Fatigue	*0.52*	***<0.0001***	0.14	**0.38**	0.10	**0.52**
Pain	*0.57*	***<0.0001***	0.35	**0.024**	−0.13	**0.43**
Neurological	*0.58*	***<0.0001***	0.35	**0.024**	−0.15	**0.35**
GI	*0.51*	***<0.0001***	0.22	**0.16**	0.32	**0.046**
Respiratory	*0.41*	***0.0001***	0.15	**0.35**	−0.050	**0.76**
Skin	*0.50*	***<0.0001***	0.40	**0.0093**	−0.054	**0.74**
Total symptoms	*0.59*	***<0.0001***	0.36	**0.0195**	−0.044	**0.79**

r = correlation coefficient. p = probability (two-sided).

reported AEs to a higher fraction of exposures. A negative relationship of AE Propensity to neurologic symptoms especially may be because controls could only be included if they did not have multiple symptoms in a category. Chemical sensitivity which related to AE Propensity relatively excludes controls with other neurological symptoms and with any symptoms with which those were correlated.

Table S1a shows the relationships between individual exposures and the AE Propensity score, for all participants, and for GWI cases and controls separately. For exposures that are materially more common in GWI cases, they may relate to AE Propensity in the total sample simply because of this. The relations in GWI cases and controls separately are not subjected to this limitation. The far-right column shows the relationship of an exposure to AE Propensity in all participants adjusted for GWI case status, via regression with robust standard errors. Particularly strong relationships occur in categories of fuels-solvents and pesticides. Controls show an apparent relationship of AE Propensity to some metals. Several individual exposures show relationships. One variable related to radiation is significant in the case-adjusted regression, with added interest based on shared direction and p values <0.2 for two of the other three variables in that category.

Negatively signed exposure correlations to AE Propensity, significant or otherwise, were not common. Among them were several exposures in the vaccine and immune globulin category; and also both copper and selenium (each of which is central to a key antioxidant system).

Table S1b shows Gulf-specific exposure queries, asked only of cases. Of note, combat and combat-stress related exposures (such as seeing Americans killed or seeing dismembered bodies) were not included in totExp, and AEs to them were not included in totAE, as the purpose was to examine predictors of drug-environment AE Propensity. These variables were, however, examined to see if they were predictors of AE Propensity. The most highly significant variable is pesticide related, with significance also present for two additional pesticide variables. Gas mask use was significant, which could cohere with pesticide use findings since gas mask use occurred in some settings of chemical alarm sounding, which could potentially reflect either actual organophosphate nerve gas (to which exposure occurred in the Gulf Conflict[57,58]), or

Table 3. Correlations among AE propensity and chemical sensitivity scores: GWI cases

	AE Propensity
	r (p)
AE Propensity	1.0
Kansas: chemsensk	0.31 (**0.047**)
UCSD: chemsenssx	0.41 (**0.0081**)
UCSD Binary	0.44 (**0.0037**)
Kansas Binary	0.26 (**0.10**)

chemsensk, having physical or mental symptoms after breathing in certain smells or chemicals; chemsenssx, chemical sensitivity (e.g., unusual sensitivity to smells); UCSD, University of California, San Diego; r, correlation coefficient; p, probability (two-sided).

Table 4. Mean AE propensity by chemical sensitivity rating

Value of measure (ordered category)	0	1	2	3	
Chemical sensitivity Self-rating measure	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	p[a]
UCSD Binary Chemical Sensitivity rating	0.15 (0.19)	0.39 (0.16)	N/A	N/A	<0.0001
Kansas Binary Chemical Sensitivity rating	0.15 (0.19)	0.35 (0.18)	N/A	N/A	<0.0001
Kansas Full Chemical Sensitivity rating	0.15 (0.19)	0.29 (0.21)	0.38 (0.14)	0.41 (0.17)	<0.01[b]

Chem, chemical; SD, standard deviation; r, correlation coefficient; p, probability (two-sided); UCSD, University of California, San Diego.
[a]For difference across categories.
[b]Some statistical commands in Stata afford different numbers of significant digits. This p value is listed as "0.00."

possibly organophosphate or other pesticide or chemical classes. (A recent study found a gene environment interaction, in which paraoxinase 1 (PON1) variants adverse to sarin detoxification coupled with reported hearing of chemical alarms were associated with a 9-fold increase in GWI.[59]) A possible consideration is that if gas masks were reused, as evidently they were, near-nose inhalation of chemical residue on the mask is a possibility. Inhalation of smoke (potentially from oil fires) was a significant predictor. Eating local food and drinking bad water were significant on univariable analyses.

A number of combat related exposures show an unadjusted relationship to AE Propensity. Factors such as forward deployment that correlated with combat were also correlated with higher environmental exposures, producing (unadjusted) appearance of a link of combat to exposure-associated outcomes. For variables with correlation p values <0.15, the right hand column reports if the variable was significant in multivariable adjustment, and whether it was included in the main model for cases (Table 6); or reports the loss of significance with the variable added to the main model. That is, combat stressors lost significance with adjustment for primary model environmental exposures. For each candidate variable not included in a multivariable model (shown later), neither significance nor borderline significance was retained when the variable was incorporated into the multivariable assessment. (In contrast, in each such instance, the variables of the main model retained significance with addition of the candidate variable.)

To maximize prediction in multivariable models, while limiting the number of included variables, composite variables were generated by summing potentially important exposures within a class. The pesticide variable included pesticides on clothes or bedding and pyrethroids. The composite fuel-fume variable included burning fuel, diesel fumes, diesel on skin, petroleum products, degreasers, and carbon monoxide. A composite radiation variable included radiation therapy, X-ray radiation, radioactive chemicals, and other radiation. Table 1 shows the mean values of these variables in all, in cases and controls, and the case-control difference. Mean values and ranges assist in interpreting coefficients in regression.

Table 5 shows the unadjusted relationships of these variables to the AE Propensity variable, in all, in GWI cases and in controls. Although the *presence* of these exposures is far greater in GWI cases, shown in

Table 5. Composite variables: Univariable relation to total AE per exposure

	All		GWI case		Control		All adjusted for GWI case	
	r	p	r	p	r	p	β (SE)	p
Composite pesticide	0.69	<0.0001	0.52	0.0005	0.69	<0.0001	0.16 (0.032)	<0.001
Composite fuel-fume	0.64	<0.0001	0.44	0.0038	0.51	0.0008	0.050 (0.013)	<0.001
Total radiation	0.54	<0.0001	0.47	0.0019	0.34	0.0298	0.038 (0.011)	0.001

Composite pesticide: sum of pesticides on clothes or bedding, and pyrethroids. Composite fuel: sum of burning fuel, diesel fumes, diesel on skin, petroleum products, degreasers, and carbon monoxide. Total radiation: sum of radiation therapy, X-ray radiation, radioactive chemicals, other radiation. The regressions use robust (heteroskedasticity-independent) standard errors.[60]
AE, adverse effect; r, correlation coefficient; β, regression coefficient; SE, standard error; p, probability (two-sided).

Table 6. AE propensity: Multivariable model assessed across groups

	All adjusted for case		Case		Control	
Exposure	b (SE)	p	b (SE)	p	β (SE)	p
Composite pesticide	0.11 (0.026)	**<0.001**	0.083 (0.025)	**0.002**	0.32 (0.085)	**0.001**
Total radiation	0.028 (0.0073)	**<0.001**	0.028 (0.0092)	**0.005**	0.031 (0.012)	**0.012**
Copper	−0.14 (0.030)	**<0.001**	−0.15 (0.033)	**<0.001**	−0.16 (0.070)	**0.026**
Composite fuel	0.027 (0.012)	**0.030**	0.021 (0.010)	**0.045**	0.0082 (0.025)	**0.74**
Case	0.070 (0.045)	0.12	N/A		N/A	
	R^2 = 0.67, p < 0.0001		R^2 = 0.60, p < 0.0001		R^2 = 0.58, p = 0.0002	

Composite pesticide: sum of pesticides on clothes or bedding, and pyrethroids. Composite fuel-fume: sum of burning fuel, diesel fumes, diesel on skin, petroleum products, degreasers, and carbon monoxide. Total radiation: sum of radiation therapy, X-ray radiation, radioactive chemicals, other radiation.
All regressions use robust (heteroskedasticity-independent) standard errors.[60] β = regression coefficient. SE = standard error. p = probability (two-sided). R^2 = "coefficient of determination," a measure of the proportion of the variance that is explained by the variables in the regression model.

Table 2, the *relationship* to the AE vulnerability variable is replicated in controls for each of the exposure classes.

Table 6 shows multivariable models, in which the exposure relationship is adjusted for other potentially relevant exposures. Table 6 shows a single multivariable model, implemented in all participants (adjusted for GWI case status), and separately in VGWI and in controls. This shows that the composite pesticide variable, the composite radiation variable, and copper exposure (inverse predictor i.e., "protective") are significant predictors in each. The composite fume-fuel exposure is significant in the total sample, and in cases, but not in controls. Its significance level is less than for the other predictors. In each model, a fairly strong R^2 is produced (0.58 or greater), with high-model significance. Of note, the R^2 remains 0.58 in the control model, omitting the non-significant composite fume-fuel variable.

Table S2 shows alternative models. Immune globulin was a significant protective predictor.

Table 7 shows candidate models specific to cases that incorporate Gulf-specific exposures. Inhaling smoke in the Gulf is substituted for the composite fuel-fume variable (Oil fire smoke was a significant problem in the Gulf.). Aerosolized depleted uranium (**DU**) exposure occurred when munitions struck vehicles (e.g., "friendly fire" episodes), and either contact with these or proximity to them (data not shown for the latter) served as independent predictors, beyond other radioactive chemical exposure. As aforementioned, gas mask use may serve as a relative proxy for organophosphate chemical exposure—either organophosphate nerve agents or pesticides that may have triggered chemical alarms and caused symptoms or other features adding concern. (As aforementioned, based on comments by veterans, there may also be a question of whether gas masks, which were reused, could have thereby served as a *source* of recurrent chemical inhalation in some settings.)

An unexpected finding was the apparent positive relation of sunscreen use in the Gulf to AE Propensity. The relationship was strong. (There was no relationship of sunscreen use *outside of* the Gulf to AE Propensity, either in controls or in Gulf War veterans; see discussion.) Of note, no combat-related or stress-related variables were independent predictors (except seeing or directly contacting destroyed enemy vehicles—a potential proxy for inhalational and/or dermal exposure to DU), often switching to a negative coefficient (non-significant); whereas model variables retained strong significance.

Table 8 shows control-specific models. These retain the composite pesticide exposure, total radiation, and copper exposures present in the models for all, and for cases. Immune globulin was a negative predictor and measles mumps rubella vaccine (**MMR**) a (weaker) positive predictor, as in analyses in the total sample (Table S2). ("Total vaccines" was not a predictor.) A modest positive relationship to metal exposure is suggested; adding iron (which is ferromagnetic, prooxidant, and relates to "ferroptosis") increases significance of all but one of the other exposures in the model, suggesting it is addressing some of the variance that curbs significance for other variables. However, the variable itself does not reach significance.

Table 7. AE propensity: Multivariable regression models, VGWI

"Main" model: Model 1			Alternative model: Model 2		
Exposure	β (SE)	p	Exposure	β (SE)	p
Composite pesticide	0.087 (0.021)	**<0.001**	Composite pesticide	0.11 (0.022)	**<0.001**
Total radiation	0.030 (0.0071)	**<0.001**	Total radiation	0.035 (0.0068)	**<0.001**
Copper	−0.13 (0.033)	**<0.001**	Copper	−0.12 (0.031)	**0.001**
Inhaled smoke from oil-well fires (in Gulf)	0.17 (0.038)	**<0.001**	Inhaled smoke from oil-well fires (in Gulf)	0.13 (0.035)	**0.001**
Gas mask	0.16 (0.051)	**0.004**	Sunscreen	0.099 (0.034)	**0.006**
$R^2 = 0.71$, $p < 0.0001$			$R^2 = 0.72$, $p < 0.0001$		

Models 3–5 each add one variable to "Main Model"

Model 3

Exposure	β (SE)	p
Composite pesticide	0.085 (0.020)	**<0.001**
Total radiation	0.029 (0.0069)	**<0.001**
Copper	−0.12 (0.031)	**<0.001**
Inhaled smoke from oil-well fires	0.14 (0.035)	**<0.001**
Gas mask	0.15 (0.047)	**0.003**
Direct contact destroyed enemy vehicles (proxy for DU)*	0.070 (0.027)	**0.014**
$R^2 = 0.74$, $p < 0.0001$		

DU = depleted uranium

*Direct contact with destroyed enemy vehicles – a proxy for potential depleted uranium inhalation exposure (since DU-girded munitions were used to penetrate/destroy enemy vehicles).

Note that substituting for this say, combat injury, air combat, ground combat, danger, saw death, saw dismemberment, these other variables have no relationship, and the strong relationships of the other variables are preserved.

Model 4			Model 5		
Sprayed pesticides in theater add separate significance to the composite pesticide exposure			Includes both gas mask (main model) and sunscreen (alternative model)		
Exposure	β (SE)	p	Exposure	β (SE)	p
Composite pesticide	0.068 (0.021)	**0.003**	Composite pesticide	0.096 (0.022)	**<0.001**
Total radiation	0.029 (0.0064)	**<0.001**	Total radiation	0.032 (0.0068)	**<0.001**
Copper	−0.12 (0.031)	**<0.001**	Copper	−0.13 (0.031)	**<0.001**
Inhaled smoke	0.15 (0.035)	**<0.001**	Inhaled smoke	0.14 (0.034)	**<0.001**
Gas mask	0.14 (0.054)	**0.013**	Gas mask	0.12 (0.058)	**0.042**
Saw pesticides sprayed in theater	0.075 (0.034)	**0.033**	Sunscreen	0.077 (0.033)	**0.024**
$R^2 = 0.75$, $p < 0.0001$			$R^2 = 0.76$, $p < 0.001$		

Model 6			Model 7		
Expanded model			Limited model		
Exposure	β (SE)	p	Exposure	β (SE)	p
Composite pesticide	0.094 (0.020)	**<0.001**	Composite pesticide	0.10 (0.025)	**<0.001**
Total radiation	0.031 (0.0070)	**<0.001**	Total radiation	0.033 (0.007)	**<0.001**
Copper	−0.11 (0.031)	**0.001**	Copper	−0.13 (0.034)	**0.001**
Inhaled smoke	0.12 (0.028)	**<0.001**	Inhaled smoke	0.15 (0.041)	**0.001**
Direct contact with destroyed enemy vehicles*	0.066 (0.024)	**0.008**			
Gas mask	0.12 (0.047)	**0.017**			

(*Continued on next page*)

Table 7. *Continued*

Model 6			Model 7		
Expanded model			Limited model		
Exposure	β (SE)	p	Exposure	β (SE)	p
Sunscreen	0.075 (0.031)	**0.021**			
R^2 = 0.78, p < 0.0001			R^2 = 0.64, p < 0.0001		

Composite pesticide: sum of pesticides on clothes or bedding, and pyrethroids; DU: depleted uranium; total radiation: sum of radiation therapy, X-ray radiation, radioactive chemicals, other radiation. *Direct contact with destroyed enemy vehicles – a proxy for potential DU inhalation exposure (since DU-girded munitions were used to penetrate/destroy enemy vehicles). Note that substituting in, say, combat-related injury, air combat, ground combat, danger/direct combat, saw Americans or Allied troops badly wounded or killed, saw dismembered bodies, these variables have no relationship, and the strong relationships of the other variables are preserved.

β, regression coefficient; SE, standard error; p, probability (two-sided); R^2, "coefficient of determination," a measure of the proportion of the variance that is explained by the variables in the regression model.

Table 9 shows results stratified at the mean participant age of 50.

In Table 9, for the total sample stratified by age using the common model, pesticides, radiation, and copper are supported in independent samples. Based on coefficients, the pesticide relationship appeared stronger in younger age, the radiation relationship stronger in older age. For other variables, coefficients are a bit stronger in younger age but variance greater and significance lower. Power is lower in age groups assessed separately. Despite this, a role for pesticides, radiation, and copper, at least, is supported in each age group separately.

Table 10 shows age-stratified results in GWI cases, using the main and alternative case-specific models. Again, based on the coefficient, the pesticide relationship appeared stronger in younger age, the radiation relationship in older age. Gas mask (main model) but not sunscreen (alternative model) relationships are preserved across stratification. Both age groups contribute to significance of the copper variable, though with a smaller sample size, significance is borderline in both groups.

Table 11 shows age-stratified results in controls. Age stratification supports the primacy of pesticides as a contributor. Copper and radiation are also supported, via significance or borderline significance in each analysis.

Given the relationship of the AE Propensity variable to skin domain symptoms in VGWI and the relation of sunscreen exposure in the Gulf to the AE Propensity variable, we examined (on an exploratory basis) the relation of AE Propensity to the Kansas skin symptom total, in those reporting and not reporting sunscreen use in theater (Table 12); and then those reporting and not reporting sunscreen use in general. Those who did not use sunscreen in theater have markedly lower AE Propensity and skin symptoms than those who did; and the relationship between skin symptoms and AE Propensity is lost in this group. There is no similar relationship for sunscreen use outside of the theater. Those without sunscreen use have lower AE Propensity than overall for cases, i.e., those with sunscreen use have higher AE Propensity. However, the relation of skin symptoms to AE Propensity is particularly low (essentially nonexistent) in those with no sunscreen exposure.

As a final step, to further assess whether predictors of AE Propensity (which can be assessed also in controls) were also predictors of self-rated chemical sensitivity (which could be examined here only in cases since only one control self-designated as having any chemical sensitivity), we assessed the key predictors in cases against the binary UCSD chemical sensitivity measure, using logistic regression with robust standard errors (Table 13).

The three primary case predictors—the pesticide variable, radiation, and inhaled smoke—were each significant predictors of the binary chemical sensitivity variable, on logistic regression. Copper and sunscreen use were not predictors. (The *sign* for the sunscreen variable was not reproduced—not shown.) Adding either copper or sunscreen, the three "primary" variables retained significance. In general, a role in cases for pesticides, and especially radiation, and smoke inhalation as predictors of chemical sensitivity is supported.

Table 8. AE propensity prediction: Control-specific model

Model 1: 4-variables			Model 2: 5-variables		
Exposure	β (SE)	P	Exposure	β (SE)	p
Composite pesticide	0.37 (0.073)	**<0.001**	Composite pesticide	0.38 (0.065)	**<0.001**
Total radiation	0.032 (0.019)	**0.019**	Total Radiation	0.031 (0.012)	**0.012**
Copper	−0.13 (0.050)	**0.012**	Copper	−0.12 (0.050)	**0.023**
Immune globulin	−0.16 (0.056)	**0.006**	MMR	0.076 (0.031)	**0.021**
			Immune globulin	−0.15 (0.050)	**0.004**
R^2 = 0.62, p = 0.0008			R^2 = 0.64, p = 0.0001		
If exclude the five participants who cited immune globulin as "unsure" (value 0.5), all are still significant but coefficients are stronger for all variables (0.41, 0.040, −0.18, −0.25) and significance is stronger for the other variables: <0.001, 0.008, 0.001; but is 0.031 for immune globulin.			If exclude the five participants who cited immune globulin exposure as "unsure", all are still significant but coefficients are strengthened for all variables, especially total radiation (β = 9.938, p = 0.006) and copper (β = −0.16, p = 0.001); and p values are strengthened for all except MMR which changes little (β = 0.082, p = 0.023).		
"Total vaccines" was not a predictor.					

Model 3: 6-variables			Model 4: 6-variables		
Exposure	β (SE)	p	Exposure	β (SE)	p
Composite pesticide	0.28 (0.063)	**<0.001**	Composite pesticide	0.25 (0.073)	**0.002**
Total Radiation	0.030 (0.011)	**0.009**	Total Radiation	0.027 (0.010)	**0.012**
Copper	−0.14 (0.055)	**0.013**	Copper	−0.15 (0.055)	**0.011**
MMR	0.082 (0.030)	**0.011**	MMR	0.086 (0.030)	**0.008**
Immune globulin	−0.12 (0.042)	**0.009**	Immune globulin	−0.12 (0.039)	**0.004**
Iron	*0.16 (0.089)*	***0.089***	*Iron + cobalt*	*0.12 (0.067)*	***0.084***
R^2 = 0.68, p = 0.0001			R^2 = 0.69, p = 0.0001		
If exclude the five participants who cited immune globulin exposure as "unsure", all are still significant but coefficients are strengthened for all variables, especially total radiation (β = 9.938, p = 0.006) and copper (β = −0.16, p = 0.001); and p values are strengthened for all except MMR which changes little (β = 0.082, p = 0.023).					

Composite pesticide: sum of pesticides on clothes or bedding, and pyrethroids. MMR, measles, mumps, rubella. Total radiation: sum of radiation therapy, X-ray radiation, radioactive chemicals, other radiation.
β = regression coefficient. SE = standard error. p = probability (two-sided). R2 = "coefficient of determination," a measure of the proportion of the variance that is explained by the variables in the regression model.

DISCUSSION

Key results

Our data affirm that AE Propensity is markedly elevated in VGWI relative to healthy controls, identifying AE Propensity as a *new feature* of GWI. Specific exposure classes that are more prevalent in VGWI predicted AE Propensity, and did so in both VGWI and controls, both validating findings in VGWI and adding relevance beyond VGWI. Predictors of AE Propensity include not only pesticides and radiation, but also combustion products. Pesticides and radiation were significant predictors in the full sample; separately in cases and controls; and separately in younger and older age groups, providing robust internal replication. Unexpectedly, reported copper exposure appeared significantly protective, in all, separately in cases and controls, and separately in younger and older age groups, in age-stratified analysis.

Additional variables were possible predictors in one or two of the "three" groups, considering cases, controls, and the total sample (adjusted for case status). Immune globulin appeared protective in the total group and in controls. Gulf-theater sunscreen appeared to be promoting in affected veterans, while sunscreen outside of this setting was not (and the sign was negative, not shown).

Table 9. AE propensity prediction. Combined VGWI and controls: Stratified by age (at mean age of 50)

	Age ≤50 N = 47		Age >50 N = 34	
Exposure	β (SE)	p	β (SE)	p
Composite pesticide	0.15 (0.043)	**0.001**	0.082 (0.028)	**0.006**
Total Radiation	0.021 (0.0093)	**0.036**	0.045 (0.011)	**<0.001**
Copper	−0.14 (0.041)	**0.002**	−0.11 (0.030)	**0.001**
Composite fuel	0.027 (0.019)	**0.17**	0.022 (0.010)	**0.044**
Case	0.071 (0.084)	**0.40**	0.066 (0.042)	**0.13**
	R^2 = 0.65, p < 0.0001		R^2 = 0.78, p < 0.0001	

Composite pesticide: sum of pesticides on clothes or bedding, and pyrethroids. Total radiation: sum of radiation therapy, X-ray radiation, radioactive chemicals, other radiation. Pesticide relationship is stronger in younger age; radiation relation appears stronger in older age.
Adding immune globulin, it was significant in younger age (p = 0.03), but not older (p = 0.56).
Adding MMR with immune globulin, it was not significant in younger, p = 0.52; but approached significance in older age, p = 0.05 (and was significant, p = 0.03, if stratification is at age 48, the median age).
N = number. β = regression coefficient. SE = standard error. p = probability (two-sided). R^2 = "coefficient of determination," a measure of the proportion of the variance that is explained by the variables in the regression model.

Interpretation/fit with existing literature

One lens with which to view findings is through twin intertwined considerations of oxidative stress and mitochondrial impairment, which are common mechanisms of toxicity for many exposure classes—irrespective of nominal mechanisms of action, for drugs/chemicals,[27–35] and extending also to radiation.[36–43] These in turn contribute to relevant downstream mechanisms of autoantibody induction,[61,62] apoptosis,[63,64] and inflammation[65]—mechanisms relevant to GWI.[4,5,8,9,17]

Pesticide exposure predicted AE Propensity in each group. Pesticides were previously shown to relate to development of multiple chemical sensitivity (**MCS**) in Gulf War veterans, OR = 12.3(95%CI:5.1–30.0).[24] In GWI cases, gas mask use and pesticides relatively attenuated the significance of each other: gas masks might serve as a proxy for organophosphate nerve gas exposure or other chemicals that cause these alarms to sound (potentially including organophosphate pesticides).

Radiation exposure predicted AE Propensity. This coheres with reports to us by nonveterans and veterans, who cite onset of chemical and electrical sensitivity following a significant EMR exposure. (Many who develop electrosensitivity do so on a backdrop of existing chemical sensitivity. Some cite *de novo* sensitivity to both chemicals and EMR, concurrently.) While this often refers to nonionizing radiation, toxicity mechanisms involving oxidative stress are shared for nonionizing and ionizing radiation (and conversely antioxidant protections are shared).[66,67] Further aligned with a role for radiation, contact with destroyed enemy vehicles—which were destroyed via DU-girded munitions, that produce aerosol/inhalational exposure and potentially dermal exposure to radioactive chemicals when they hit a target—was a possible independent predictor. Other combat and combat stress-related exposures bore no independent relationship.

Fuels-fumes were not a material independent predictor in controls, though these were a predictor in the total sample, and inhaling smoke (e.g., from burning oil fires) was a predictor in cases.

Pesticides,[68–77] across major classes, as well as radiation across the spectrum[78,79] can depress activity of critical endogenous antioxidant systems, like glutathione, superoxide dismutase and catalase, perhaps by consuming antioxidants. (Results vary according to specifics of the study: such systems can in certain conditions, be adaptively upregulated.[80]) This could be one factor contributing to their role. Moreover, radiation can also depress levels of melatonin,[81–94] which though better known for its relation to sleep, has critical antioxidant functions, and has been shown to defend against toxicity not only from radiation itself[66,95–115] (across the electromagnetic spectrum—nonionizing and ionizing[66,67]) but from toxicity of many drugs and chemicals,[116–151] including toxicity by pyrethroids[152] and organophosphates[153–155]—which was present in nerve gas to which some personnel were exposed, and in key pesticides used in the Persian Gulf. In a French study including >700 persons with nonionizing-radiation sensitivity

Table 10. Total AE propensity, GWI Case regression models: Stratified by age (at mean age of 50)

	Main Model			
	Age ≤50 N = 23		Age >50 N = 18	
Exposure	β (SE)	p	β (SE)	p
Composite pesticide	0.13(0.033)	**0.001**	0.044 (0.031)	**0.18**
Total radiation	0.022 (0.0089)	**0.022**	0.048 (0.011)	**0.001**
Inhaled smoke from oil-well fires	0.21 (0.069)	**0.007**	0.088 (0.050)	**0.103**
Copper	−0.13 (0.063)	**0.055**	−0.080 (0.042)	**0.082**
Gas mask	0.19 (0.052)	**0.002**	0.13 (0.061)	**0.036**
	R^2 = 0.75, p not calculated		R^2 = 0.82, p < 0.0001	
	Alternative Model			
	Age ≤50 N = 23		Age >50 N = 18	
Exposure	β (SE)	p	β (SE)	p
Composite pesticide	0.14 (0.036)	**0.001**	0.083 (0.020)	**0.001**
Total radiation	0.024 (0.008)	**0.007**	0.057 (0.012)	**0.001**
Inhaled smoke from oil-well fires	0.27 (0.066)	**0.023**	0.098 (0.079)	**0.24**
Copper	−0.11 (0.067)	**0.12**	−0.086 (0.030)	**0.013**
Sunscreen	0.070 (0.056)	**0.23**	0.11 (0.039)	**0.013**
	R^2 = 0.74, p < 0.0001		R^2 = 0.84, p = 0.0004	

Composite pesticide: sum of pesticides on clothes or bedding, and pyrethroids. Total radiation: sum of radiation therapy, X-ray radiation, radioactive chemicals, other radiation.

In cases too, the pesticide relationship (and gas mask relationship) appears stronger in younger age; radiation relationship (best on the coefficient) appears stronger in older age.

Inhaled smoke is far stronger in younger age. If the split is at the median rather than the mean, gas mask use is significant in younger (p = 0.003) and older (p = 0.04) age; copper is significant in older age, p = 0.019 and – with a stronger coefficient – almost significant in younger age (p = 0.06). Pesticides still lose significance in older age (younger personnel may have been involved in actual pesticide application in theater), and with the smaller sample and younger age, significance for radiation is lost (p = 0.02).

N = number. β = regression coefficient. SE = standard error. p = probability (two-sided). R^2 = "coefficient of determination," a measure of the proportion of the variance that is explained by the variables in the regression model.

(electrosensitivity), many with chemical sensitivity, a depressed ratio of 24-h excretion of a urine melatonin metabolite (6-hydroxymelatonin sulfate) relative to creatinine was a biomarker.[156] Radiation and radioactive chemicals[157] can also depress activity of other endogenous antioxidant systems, such as the glutathione system,[158–165] which also defends against radiation and drug-chemical-environmental oxidative stress (**OS**) injury[160,166–178] (including from pesticides-solvents).[179] (In turn, low glutathione peroxidase is linked to drug and chemical intolerance.[175])

Depressed antioxidant defenses may explain why pesticide and radiation exposures that can promote development of MCS also can set people up for developing electrosensitivity following chemical or especially significant radiation exposures. Indeed, chemical-induced depression in antioxidant systems has been shown to be involved in increased vulnerability to toxicity of radiation.[180] A role for antioxidant defenses in chemical sensitivities is supported by genetic evidence relating an adverse polymorphism of superoxide dismutase 2 (**SOD2**) to chemical sensitivity,[49,181] and evidence of depressed glutathione levels, depressed catalase and glutathione S transferase activities in patients with MCS,[156,182] and the aforementioned findings with respect to melatonin metabolite excretion.

Both pesticides[183–203] and radiation are reported to adversely affect mitochondria,[40,41,46,202–211] as do radioactive chemicals, including DU.[212–214] Impaired mitochondria amplify free radical production[51,52] and risks with many exposures. Again, AEs often involve mitochondrial compromise and OS.[27–35]

Table 11. Total AE Propensity, control regression models: Stratified by age (at mean age of 50)

	Controls			
	Age ≤50 N = 24		Age >50 N = 16	
Exposure	β (SE)	p	β (SE)	p
Composite pesticide	0.55 (0.089)	**<0.001**	0.26 (0.025)	**<0.001**
Total Radiation	0.029 (0.014)	**0.053**	0.050 (0.020)	**0.032**
Copper	−0.083 (0.038)	**0.040**	−0.13 (0.033)	**0.002**
Immune globulin	−0.050 (0.085)	**0.56**	−0.13 (0.050)	**0.028**
	R^2 = 0.71, p < 0.0001		R^2 = 0.69, p not defined	

Composite pesticide: sum of pesticides on clothes or bedding, and pyrethroids. Total radiation: sum of radiation therapy, X-ray radiation, radioactive chemicals, other radiation.
Pesticide relationship is stronger in younger age, other relationships are stronger in older age.
β = regression coefficient. SE = standard error. p = probability (two-sided). R^2 = "coefficient of determination," a measure of the proportion of the variance that is explained by the variables in the regression model.

(Perhaps not surprisingly given potential for mitochondrial injury and impaired antioxidant defenses, both pesticides[76,215–222] and radiation produce OS at least acutely.[39,41,66,96,98–101,105,107,109,210,223–256])

Pesticides and radiation have also each been shown to alter membrane properties,[184,201,257–265] the latter finding replicated across many frequencies and lifeforms.[205,211,230,266–274] This extends to radioactive chemicals (including uranium).[275]

Inhaled combustion products were predictors in VGWI, who had more prospects for significant smoke inhalation exposure, via exposure to oil fire smoke. Smoke/combustion products and inhaled particulates are also linked to OS[276–280] and mitochondrial injury.[277,281] Delta psi, the mitochondrial membrane potential, which relates to apoptosis risk, is affected by combustion products/smoke,[281] radiation,[281] and pesticides.[188,201,282–285]

Table 12. Relation of AE propensity to skin symptoms (Kansas criteria), as a function of sunscreen use In and out of theater, in GWI cases

Sunscreen in Gulf Theater	No Sunscreen in Theater N = 16		Yes Sunscreen in Theater N = 23	
AE Propensity: Mean (SD)	0.28 (0.16)		0.37 (0.18)	
Skin symptoms: Mean (SD)	1.2 (1.6)		2.4 (2.1)	
Correlation of skin symptoms to AE Propensity	r	p	r	p
	0.015	**0.96**	0.48	**0.020**
	Sunscreen use, Not Gulf-specific			
Sunscreen, Not Gulf	No Sunscreen, General N = 20		Sunscreen, General N = 19	
AE Propensity: Mean (SD)	*0.35 (0.20)*		*0.33 (0.15)*	
Skin symptoms: Mean (SD)	*1.9 (2.4)*		*1.7 (1.4)*	
Correlation of skin symptoms to AE Propensity	*r*	*p*	*r*	*p*
	0.49	*0.029*	*0.46*	*0.046*

Those citing no Gulf-theater sunscreen exposure have lower AE Propensity, half the Kansas skin symptoms score; and no correlation of AE Propensity to skin symptoms. In contrast, in those with Gulf sunscreen exposure, there is a strong correlation between these, nearly 0.5 (with p = 0.020). Of note, there is no such disparity with sunscreen use outside of the Gulf (in which with and without are associated with a significant correlation of skin symptoms to AE Propensity).
N, number; r, correlation coefficient; p, probability (two-sided); SD, standard deviation.

Table 13. Multivariable assessment of chemical sensitivity variables in cases using the model optimized for Total AE Propensity

UCSD binary chemical sensitivity			Kansas, full chemical sensitivity		
Exposure	β (SE)	p	Exposure	β (SE)	p
Composite pesticide	0.94 (0.45)	**0.037**	Composite pesticide	−0.15 (0.42)	**0.72**
Total radiation	0.38 (0.19)	**0.048**	Total radiation	0.47 (0.20)	**0.021**
Inhale smoke	3.3 (1.4)	**0.016**	Inhale smoke	3.0 (0.85)	**<0.001**
R^2 = 0.25, p = 0.013			Pseudo R^2 = 0.14, p = 0.0056		
UCSD binary			**Kansas, full**		
Exposure	β (SE)	p	Exposure	β (SE)	p
Composite pesticide	0.96 (0.47)	**0.039**	Composite pesticide	−0.14 (0.42)	**0.74**
Total radiation	0.39 (0.20)	**0.044**	Total radiation	0.48 (0.22)	**0.024**
Inhale smoke	3.2 (1.3)	**0.016**	Inhale smoke	2.9 (0.82)	**0.001**
Copper	0.59 (0.81)	**0.47**	Copper	−0.48 (0.66)	**0.47**
R^2 = 0.25, p = 0.013			Pseudo R^2 = 0.15, p = 0.012		
Adding gas mask use, it is not a predictor: p = 0.76.			Substituting the saw-pesticides-sprayed variable, the pesticide becomes 0.88 (0.60) 0.14; the variables retain similar coefficients, with p = 0.26 and 0.002.		

Composite pesticide: sum of pesticides on clothes or bedding, and pyrethroids. Total radiation: sum of radiation therapy, X-ray radiation, radioactive chemicals, other radiation.
Regression approach: Logistic regression (robust standard errors) for the UCSD Binary Chemical Sensitivity variable; ordinal logit regression (robust standard errors) for the Kansas, Full Chemical Sensitivity measure.
β, regression coefficient; SE, standard error; p, probability (two-sided); R^2, "coefficient of determination," a measure of the proportion of the variance that is explained by the variables in the regression model.

Thus, implicated agents may markedly enhance vulnerability to toxicity from many exposures, encompassing many drugs, chemicals and radiation exposures that can further impair mitochondrial function, and/or cause OS, which can promote apoptosis, or alter membrane properties (involved in barrier function, mitochondrial function, and apoptosis regulation).

OS, induced by the above exposures, can enhance triggering of immune and autoimmune reactions[286–298] (hence effectiveness of adjuvants in vaccines), and some triggered AEs may have immune mediation; Gulf War veterans have been shown to have increased autoantibodies,[5,17] as do persons with radiation AEs,[156] and epidemiological evidence associates pesticide exposure with autoimmune conditions.[299,300] (It is a prediction of the present paper that if radiation has not already been shown to do so, it will. Nonionizing radiation sensitivity has been tied to increased autoantibodies.[156]) This might account for the (tentatively supported) protective association of immune globulin (gamma globulin), which was given to some Persian Gulf War personnel,[301,302] to AE Propensity—a finding supported in controls and the total sample. Its use has been associated with improvement in experimental and naturally occurring autoimmune conditions.[303,304] The association with protection must be considered tentative—but could suggest a candidate treatment to try.

An unexpected finding was the apparent protective association of copper-exposure against AE Propensity, seen in cases, controls, the full sample and on age-stratified analysis. Excess copper can cause prooxidant injury; however, copper intake in US adolescents and adults has been reported to be low[305]; perhaps copper-zinc SOD may depend, in this setting, on adequacy of copper. Moreover, though able to cause prooxidant effects, copper can also increase activity of catalase and increase gene expression for multiple critical antioxidants and antioxidant regulators, including SOD1 (copper-zinc SOD), glutathione peroxidase, glutathione-S-transferase, Nrf2 (viewed as a master antioxidant regulator), and Kelch-like ECH associated protein 1a (Keap-1a)—albeit, here assessed in a nonmammal organism.[306] In a seminar for medical providers focused on genetic predictors of health problems,[307] a family with extreme multiple chemical intolerance was described, members of which were found to lack remarkable findings in other antioxidant systems but showed strong multiple adverse polymorphisms related to copper-associated detoxification systems (copper chaperone antioxidant-1, "Atox-1").

Cell copper accumulation is reported to be higher in linoleate supplemented cells[308] (however, this study was done in microbes). Linoleic acid is the precursor for arachidonic acid, and we have found many arachidonic acid products to be markedly depressed in VGWI[4,309]—suggesting, but not confirmative for, the possibility of depressed levels of linoleate. Following a speculative line of reasoning, if veterans have reduced linoleic acid, leading to reduced copper retention, those affected with GWI may have relative shortfalls in cellular copper—potentially affecting antioxidant activity,[310] as earlier, and mitochondrial function (which is low in VGWI,[6] as below). Frank deficiency may be unlikely; copper deficiency is linked to peripheral neuropathy (many VGWI indeed cite neuropathic symptoms), ataxia (a feature in some VGWI[311])—and sometimes motor neuron problems (which three studies reported to be present in excess in GWI, in the first decade or so following Gulf deployment[312–314]). But it is also linked to myelopathy and anemia, which are not reported to be characteristic in VGWI. Of note, the fatty acid changes consistent with those in GWI (potentially opposed to copper uptake) are also reportedly opposed to accumulation of radioactive chemicals (in microbes),[315] suggesting the possibility that observed alterations in VGWI might be adaptive.

The redox activity of copper is essential for mitochondrial enzyme activity,[310] which is depressed in GWI.[6] Additionally, copper deficiency may enhance vulnerability to apoptosis[316]; altered apoptosis regulation has repeatedly emerged as altered in GWI.[317–319] On the flip side, copper is a source of endogenous free radicals[310]; endogenous copper may be mobilized during periods of OS, and may be "particularly dangerous" in settings of mitochondrial dysfunction.[320] A number of agents that cause OS act synergistically with copper to depress mitochondrial membrane potential.[320] Though no definite inferences are possible, assessment of copper status may be merited in VGWI.

Gulf exposure to sunscreen was apparently adverse, an intriguing finding with both mundane and interesting potential bases. This could be a chance finding. Breakdown products arising from desert heat (and nighttime cold) exposure could have conferred problems themselves or with other exposures. The specific sunscreen(s) that used in theater could have had components, or breakdown products, that were a problem themselves or with other exposures. The sunscreen could have afforded a depot and conduit for other chemicals to persist and continue to penetrate the skin. Other oxidative stressor exposures combined with sunscreen application could have led to an immune reaction by mechanisms discussed above.

More interesting hypotheses relate to reduced UV-B exposure and its implications for production of vitamin D and also melanin—which confers antioxidant protection operating locally in the skin.[321,322] UV-B induces production of vitamin D,[323] which is critical for its benefits to OS, apoptosis, autoimmunity, muscle strength, and mitochondrial function. Vitamin D protects against radiation injury including radiation-induced cell senescence and cell/keratinocyte apoptosis.[324,325] It may decrease oxidative injury in GWI-relevant organs including the gastrointestinal tract.[326] It is linked to reduced development of autoimmunity,[327–330] which is increased in VGWI and related to neurological and pain symptoms.[5,17] Improved vitamin D status enhances mitochondrial energy production in muscle,[331] and is linked to muscle strength including in RCTs[332,333] and reduced pain in some studies,[334,335] potentially contributing to the greater impact of Gulf-sunscreen-abstinence-presence on the relation of AE Propensity to symptoms in the neurological and pain domains, relative to others (besides skin). Activation of the vitamin D receptor (e.g., by vitamin D) inhibits energy loss-restoration injury to tissue (reperfusion injury), by "reducing oxidative stress, and inhibiting apoptosis and autophagy dysfunction-mediated cell death".[336] Vitamin D activates the Nrf2-Keap1 ("master") antioxidant pathway.[337] It is reported to reverse age-related increases in microglial activation that may contribute to brain effects such as those in aging (also relevant to the neurological domain).[338] So having endogenous UV-B triggered vitamin D on board at the time of other Gulf-relevant exposures—many known to trigger OS, cell energy compromise, autoimmune triggering, and apoptosis—may have protected against injury at the time. This may protect against later symptoms either from exposure-induced worsening of oxidative and mitochondrial mechanisms, e.g., already impaired by Gulf-relevant exposures—and/or some AEs may involve immune-autoimmune systems as suggested by apparent protection by immune globulin.

Sunscreen (and associated disruption of skin access to UV-B) also reduces production of melanin which confers antioxidant protections to the skin.[321,322] This would account for why sunscreen exposure was apparently detrimental selectively in theater, the setting with the high load of toxins against which UV-induced products protect. AE Propensity in VGWI was most strongly related to the skin domain among Kansas GWI domains.

Limitations of the study

This analysis has limitations. Findings are cross-sectional and causality and in some cases temporality is difficult to infer, particularly for nonveteran participants. (Virtually all veterans describe themselves as having had health that was "very good" or "excellent" at the time of their participation in the Gulf War.[6] Early Gulf experiences are relatively likely to precede health problems.) Information is based on self-report, which may be subject to recall and recording bias.

Selection of participants was not contingent on any specific exposure, so the power to assess the impact of different exposures differs. Of note, participants did not know that we would examine the relation of reported exposures to reported AE Propensity, so at least that expectation will not have influenced reporting.

VGWI are a comparatively heavily exposed group, which benefits ability to see exposure relations for a number of exposures. However, the number of participants, though sizable for a study of VGWI that also assessed objective markers (presented separately)[4,12,55,309] and with excellent power for paired analyses, is limited in the number of exposures that can be meaningfully included in a regression, particularly where subgroup analyses are also conducted. As for all new findings, authority of findings will rest on replication. In this vein, internal replication of major findings—shown in GWI cases and controls, younger and older participants—materially enhances confidence in key findings. The fit of the pesticide findings with chemical sensitivity literature; and the radiation finding with emerging data in the electrosensitivity and radiosensitivity sphere,[156,339,340] further reinforce the likelihood that these are genuine risk factors. Combustion products, which were weaker and less consistent predictors here, have been highlighted in MCS.[341]

Relevant risk factors may have been missed. Insufficient participants with (or without) an exposure, or existence of a vulnerable subgroup *vis-à-vis* that exposure, may necessitate a larger sample or different analysis approach to see effects. Though the exposure assessments were extensive, they are not all-inclusive.

Evaluation of AE propensity should be extended in future studies to other military and veteran groups, as well as to potentially exposed civilian subgroups. However, replication within this study of key findings in nonveteran controls as well as GWI cases, and in younger and older age strata, suggests these findings likely generalize.

Heightened AE Propensity may be viewed as a new feature of GWI, distinct from presence of ongoing symptoms. Concordance of exposure relationships to AE Propensity between VGWI and controls serves as a reminder that findings in the unique Gulf War veteran population can offer vital information of relevance to the rest of us. Exposure to pesticides, radiation, and perhaps combustion products may render some people more susceptible to AEs spanning many classes of exposure. Additional studies are needed to determine whether exposures subsequent to the Gulf, in affected veterans, may not only precipitate time-limited worsening, but may actually magnify severity of the overall illness in VGWI, as some veterans report.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.107363.

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AUTHOR CONTRIBUTIONS

B.G. designed and oversaw conduction of the study, performed the initial analyses, drafted the initial paper, and participated in the investigation, supervision, administration, and funding acquisition for the project. J.H. participated in validation of statistical results, review and editing of the manuscript, as well as administrative aspects of manuscript submission. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

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REFERENCES

1. Binns, J.H., Cherry, N., Golomb, B.A., Graves, J.C., Haley, R.W., Knox, M.L., Meggs, W.J., Pellier, P.J., Robinson, S.L., Smithson, S., and Steele, L. (2004). Research Advisory Committee on Gulf War Veterans' Illnesses: Scientific Progress in Understanding Gulf War Veterans' Illnesses: Report and Recommendations.

2. Binns, J.H., Barlow, C., Bloom, F.E., Clauw, D.J., Golomb, B.A., Graves, J.C., Hardie, A., Knox, M.L., Meggs, W.J., Nettleman, M.D., et al. (2008). Gulf war illness and the health of gulf war veterans. Scientific Findings and Recommendations (U.S. Government Printing Office).

3. Steele, L. (2000). Prevalence and patterns of Gulf War illness in Kansas veterans: association of symptoms with characteristics of person, place, and time of military service. Am. J. Epidemiol. *152*, 992–1002.

4. Golomb, B.A., Koslik, H.J., Christians, U., Ritchie, J., Wilson, P., Elkins, N., Klawitter, J., Klawitter, J., Smith, D., and Repine, J.E. (2019). Depressed prostaglandins and leukotrienes in veterans with Gulf War illness. J. Environ. Sci. Health. B *54*, 623–639. https://doi.org/10.1080/03601234.2019.1596001.

5. Abou-Donia, M.B., Conboy, L.A., Kokkotou, E., Jacobson, E., Elmasry, E.M., Elkafrawy, P., Neely, M., Bass, C.R.'D., and Sullivan, K. (2017). Screening for novel central nervous system biomarkers in veterans with Gulf War Illness. Neurotoxicol. Teratol. *61*, 36–46. https://doi.org/10.1016/j.ntt.2017.03.002.

6. Koslik, H.J., Hamilton, G., and Golomb, B.A. (2014). Mitochondrial dysfunction in gulf war illness revealed by 31Phosphorus magnetic resonance spectroscopy: a case-control study. PLoS One *9*, e92887.

7. Haley, R.W., Charuvastra, E., Shell, W.E., Buhner, D.M., Marshall, W.W., Biggs, M.M., Hopkins, S.C., Wolfe, G.I., and Vernino, S. (2013). Cholinergic autonomic dysfunction in veterans with Gulf War illness: confirmation in a population-based sample. JAMA Neurol. *70*, 191–200. https://doi.org/10.1001/jamaneurol.2013.596.

8. Johnson, G.J., Slater, B.C.S., Leis, L.A., Rector, T.S., and Bach, R.R. (2016). Blood biomarkers of chronic inflammation in gulf war illness. PLoS One *11*, e0157855. https://doi.org/10.1371/journal.pone.0157855.

9. James, L., Engdahl, B., Johnson, R., and Georgopoulos, A. (2019). Gulf war illness and inflammation: association of symptom severity with C-reactive protein. J. Neurol. Neuromedicine *4*, 15–19.

10. Shetty, G.A., Hattiangady, B., Upadhya, D., Bates, A., Attaluri, S., Shuai, B., Kodali, M., and Shetty, A.K. (2017). Chronic oxidative stress, mitochondrial dysfunction, Nrf2 activation and inflammation in the Hippocampus accompany heightened systemic inflammation and oxidative stress in an Animal model of gulf war illness. Front. Mol. Neurosci. *10*, 182. https://doi.org/10.3389/fnmol.2017.00182.

11. Abdullah, L., Evans, J.E., Joshi, U., Crynen, G., Reed, J., Mouzon, B., Baumann, S., Montague, H., Zakirova, Z., Emmerich, T., et al. (2016). Translational potential of long-term decreases in mitochondrial lipids in a mouse model of Gulf War Illness. Toxicology *372*, 22–33. https://doi.org/10.1016/j.tox.2016.10.012.

12. Golomb, B.A., Koslik, H.J., Han, J.H., Preger Guida, A.H., Hamilton, G., and Kelley, R.I. (2021). A pilot study of bioenergetic marker relationships in gulf war illness: phosphocreatine recovery vs. citric acid cycle intermediates. Int. J. Environ. Res. Public Health *18*, 1635. https://doi.org/10.3390/ijerph18041635.

13. Golier, J.A., Schmeidler, J., Legge, J., and Yehuda, R. (2007). Twenty-four hour plasma cortisol and adrenocorticotropic hormone in gulf war veterans: relationships to Posttraumatic stress disorder and health symptoms. Biol. Psychiatry *62*, 1175–1178.

14. Golier, J.A., Schmeidler, J., and Yehuda, R. (2009). Pituitary response to metyrapone in

Gulf War veterans: relationship to deployment, PTSD and unexplained health symptoms. Psychoneuroendocrinology *34*, 1338–1345. https://doi.org/10.1016/j.psyneuen.2009.04.004.

15. Haley, R.W., Vongpatanasin, W., Wolfe, G.I., Bryan, W.W., Armitage, R., Hoffmann, R.F., Petty, F., Callahan, T.S., Charuvastra, E., Shell, W.E., et al. (2004). Blunted circadian variation in autonomic regulation of sinus node function in veterans with Gulf War syndrome. Am. J. Med. *117*, 469–478.

16. Jaquess, K.J., Allen, N., Chun, T.J., Crock, L., Zajdel, A.A., Reinhard, M.J., and Costanzo, M.E. (2021). The relationship between Gulf War Illness symptom severity and heart rate variability: a pilot study. Life Sci. *280*, 119663. https://doi.org/10.1016/j.lfs.2021.119663.

17. Vojdani, A., and Thrasher, J.D. (2004). Cellular and humoral immune abnormalities in Gulf War veterans. Environ. Health Perspect. *112*, 840–846.

18. Abou-Donia, M.B., Krengel, M.H., Lapadula, E.S., Zundel, C.G., LeClair, J., Massaro, J., Quinn, E., Conboy, L.A., Kokkotou, E., Nguyen, D.D., et al. (2021). Sex-based differences in plasma autoantibodies to central nervous system proteins in gulf war veterans versus healthy and symptomatic controls. Brain Sci. *11*, 148. https://doi.org/10.3390/brainsci11020148.

19. Gray, G.C., Reed, R.J., Kaiser, K.S., Smith, T.C., and Gastañaga, V.M. (2002). Self-reported symptoms and medical conditions among 11,868 gulf war-era veterans: the Seabee health study. Am. J. Epidemiol. *155*, 1033–1044.

20. Thomas, H.V., Stimpson, N.J., Weightman, A.L., Dunstan, F., and Lewis, G. (2006). Systematic review of multi-symptom conditions in Gulf War veterans. Psychol. Med. *36*, 735–747.

21. Unwin, C., Blatchley, N., Coker, W., Ferry, S., Hotopf, M., Hull, L., Ismail, K., Palmer, I., David, A., and Wessely, S. (1999). Health of UK servicemen who served in Persian Gulf War. Lancet *353*, 169–178.

22. Cherry, N., Creed, F., Silman, A., Dunn, G., Baxter, D., Smedley, J., Taylor, S., and Macfarlane, G.J. (2001). Health and exposures of United Kingdom Gulf war veterans. Part I: the pattern and extent of ill health. Occup. Environ. Med. *58*, 291–298.

23. Bell, I.R., Warg-Damiani, L., Baldwin, C.M., Walsh, M.E., and Schwartz, G.E. (1998). Self-reported chemical sensitivity and wartime chemical exposures in Gulf War veterans with and without decreased global health ratings. Mil. Med. *163*, 725–732.

24. Reid, S., Hotopf, M., Hull, L., Ismail, K., Unwin, C., and Wessely, S. (2001). Multiple chemical sensitivity and chronic fatigue syndrome in British Gulf War veterans. Am. J. Epidemiol. *153*, 604–609.

25. Nass, M. (2009). Symptom patterns and treatment strategies for fibromyalgia, GW illness and military post-vaccination patients. In Research Advisory Committee on Gulf War Veterans' Illnesses. Presentation to Research Advisory Committee on Gulf War Veterans' Illnesses. June 29-30, Washington, D.C.

26. Department of Veterans Affairs (2021). Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.

27. Wallace, K.B., and Starkov, A.A. (2000). Mitochondrial targets of drug toxicity. Annu. Rev. Pharmacol. Toxicol. *40*, 353–388.

28. Boelsterli, U.A., and Lim, P.L.K. (2007). Mitochondrial abnormalities - a link to idiosyncratic drug hepatotoxicity? Toxicol. Appl. Pharmacol. *220*, 92–107.

29. Varga, Z.V., Ferdinandy, P., Liaudet, L., and Pacher, P. (2015). Drug-induced mitochondrial dysfunction and cardiotoxicity. Am. J. Physiol. Heart Circ. Physiol. *309*, H1453–H1467. https://doi.org/10.1152/ajpheart.00554.2015.

30. Anglin, R., Rosebush, P., and Mazurek, M. (2012). Psychotropic medications and mitochondrial toxicity. Nat. Rev. Neurosci. *13*, 650. https://doi.org/10.1038/nrn3229-c1.

31. Tafazoli, S., Spehar, D.D., and O'Brien, P.J. (2005). Oxidative stress mediated idiosyncratic drug toxicity. Drug Metab. Rev. *37*, 311–325.

32. Amin, A., and Hamza, A.A. (2005). Oxidative stress mediates drug-induced hepatotoxicity in rats: a possible role of DNA fragmentation. Toxicology *208*, 367–375. https://doi.org/10.1016/j.tox.2004.11.039.

33. Verma, P., Bhattacharya, S.N., Banerjee, B.D., and Khanna, N. (2012). Oxidative stress and leukocyte migration inhibition response in cutaneous adverse drug reactions. Indian J. Dermatol. Venereol. Leprol. *78*, 664. https://doi.org/10.4103/0378-6323.100519.

34. Das, G.C., Bacsi, A., Shrivastav, M., Hazra, T.K., and Boldogh, I. (2006). Enhanced gamma-glutamylcysteine synthetase activity decreases drug-induced oxidative stress levels and cytotoxicity. Mol. Carcinog. *45*, 635–647. https://doi.org/10.1002/mc.20184.

35. McMillian, M., Nie, A., Parker, J.B., Leone, A., Kemmerer, M., Bryant, S., Herlich, J., Yieh, L., Bittner, A., Liu, X., et al. (2005). Drug-induced oxidative stress in rat liver from a toxicogenomics perspective. Toxicol. Appl. Pharmacol. *207*, 171–178. https://doi.org/10.1016/j.taap.2005.02.031.

36. Wan, X.S., Ware, J.H., Zhou, Z., Donahue, J.J., Guan, J., and Kennedy, A.R. (2006). Protection against radiation-induced oxidative stress in cultured human epithelial cells by treatment with antioxidant agents. Int. J. Radiat. Oncol. Biol. Phys. *64*, 1475–1481.

37. von Deutsch, A.W., Mitchell, C.D., Williams, C.E., Dutt, K., Silvestrov, N.A., Klement, B.J., Abukhalaf, I.K., and von Deutsch, D.A. (2005). Polyamines protect against radiation-induced oxidative stress. Gravit. Space Biol. Bull. *18*, 109–110.

38. Robbins, M.E.C., and Zhao, W. (2004). Chronic oxidative stress and radiation-induced late normal tissue injury: a review. Int. J. Radiat. Biol. *80*, 251–259.

39. Zhang, Q.J., and Wu, K. (2004). [Biological oxidative stress induced by electromagnetic irradiation]. Space Med. Med. Eng. *17*, 152–156.

40. Prithivirajsingh, S., Story, M.D., Bergh, S.A., Geara, F.B., Ang, K.K., Ismail, S.M., Stevens, C.W., Buchholz, T.A., and Brock, W.A. (2004). Accumulation of the common mitochondrial DNA deletion induced by ionizing radiation. FEBS Lett. *571*, 227–232.

41. Yoshida, T., Goto, S., Kawakatsu, M., Urata, Y., and Li, T.S. (2012). Mitochondrial dysfunction, a probable cause of persistent oxidative stress after exposure to ionizing radiation. Free Radic. Res. *46*, 147–153. https://doi.org/10.3109/10715762.2011.645207.

42. Hampson, R.K., Medina, M.A., and Olson, M.S. (1982). The use of high-energy microwave irradiation to inactivate mitochondrial enzymes. Anal. Biochem. *123*, 49–54.

43. Burlaka, A., Selyuk, M., Gafurov, M., Lukin, S., Potaskalova, V., and Sidorik, E. (2014). Changes in mitochondrial functioning with electromagnetic radiation of ultra high frequency as revealed by electron paramagnetic resonance methods. Int. J. Radiat. Biol. *90*, 357–362. https://doi.org/10.3109/09553002.2014.899448.

44. Dalle Carbonare, M., and Pathak, M.A. (1992). Skin photosensitizing agents and the role of reactive oxygen species in photoaging. J. Photochem. Photobiol., B *14*, 105–124.

45. Ouédraogo, G., Morlière, P., Santus, R., Miranda, and Castell, J.V. (2000). Damage to mitochondria of cultured human skin fibroblasts photosensitized by fluoroquinolones. J. Photochem. Photobiol., B *58*, 20–25.

46. Ortiz, F., Acuña-Castroviejo, D., Doerrier, C., Dayoub, J.C., López, L.C., Venegas, C., García, J.A., López, A., Volt, H., Luna-Sánchez, M., and Escames, G. (2015). Melatonin blunts the mitochondrial/NLRP3 connection and protects against radiation-induced oral mucositis. J. Pineal Res. *58*, 34–49. https://doi.org/10.1111/jpi.12191.

47. Burlaka, A.P., Druzhyna, M.O., Vovk, A.V., and Lukin, S.M. (2016). Disordered redox metabolism of brain cells in rats exposed to low doses of ionizing radiation or UHF electromagnetic radiation. Exp. Oncol. *38*, 238–241.

48. De Luca, C., Thai, J.C.S., Raskovic, D., Cesareo, E., Caccamo, D., Trukhanov, A., and Korkina, L. (2014). Metabolic and genetic screening of electromagnetic hypersensitive subjects as a feasible tool for diagnostics and intervention. Mediators Inflamm. *2014*, 924184. https://doi.org/10.1155/2014/924184.

49. Cui, X., Lu, X., Hiura, M., Oda, M., Miyazaki, W., and Katoh, T. (2013). Evaluation of genetic polymorphisms in patients with multiple chemical sensitivity. PLoS One *8*, e73708. https://doi.org/10.1371/journal.pone.0073708 PONE-D-13-19565.

50. Lee, H.C., and Wei, Y.H. (1997). Role of mitochondria in human aging. J. Biomed. Sci. *4*, 319–326.

51. Wei, Y.H. (1998). Oxidative stress and mitochondrial DNA mutations in human aging. Proc. Soc. Exp. Biol. Med. *217*, 53–63.

52. Genova, M.L., Pich, M.M., Bernacchia, A., Bianchi, C., Biondi, A., Bovina, C., Falasca, A.I., Formiggini, G., Castelli, G.P., and Lenaz, G. (2004). The mitochondrial production of reactive oxygen species in relation to aging and pathology. Ann. N. Y. Acad. Sci. *1011*, 86–100.

53. Fadic, R., and Johns, D.R. (1996). Clinical spectrum of mitochondrial diseases. Semin. Neurol. *16*, 11–20.

54. Nonaka, I. (1992). Mitochondrial diseases. Curr. Opin. Neurol. Neurosurg. *5*, 622–632.

55. Golomb, B.A., Devaraj, S., Messner, A.K., Koslik, H.J., Han, J.H., and Yik, B. (2021). Lower blood malondialdehyde is associated with past pesticide exposure: findings in Gulf War illness and healthy controls. Mil. Med. Res. *8*, 46. https://doi.org/10.1186/s40779-021-00337-0.

56. Golomb, B.A., Nguyen, E., and Dinkeloo, E. (2020). Radiation exposure Predicts reported vaccine adverse effects in veterans with gulf war illness. Int. J. Environ. Res. Public Health *17*, 7136. https://doi.org/10.3390/ijerph17197136.

57. General Accounting Office. (2004). Gulf War Illnesses: DOD's Conclusions about U.S. Troops' Exposure Cannot Be Adequately Supported. GAO report number GAO-04-159. http://www.gao.gov/htext/d04159.html.

58. Gillert, D.J. (1997). DoD Says 98,910 Exposed to Low Levels of Nerve Agent. American Forces Press Service (US Department of Defense).

59. Haley, R.W., Kramer, G., Xiao, J., Dever, J.A., and Teiber, J.F. (2022). Evaluation of a gene-environment interaction of PON1 and low-level nerve agent exposure with gulf war illness: a prevalence case-control study drawn from the U.S. Military health Survey's National population sample. Environ. Health Perspect. *130*, 57001. https://doi.org/10.1289/ehp9009.

60. White, H. (1980). A heteroskedasticity-consistent covariance matrix estimator and a direct test for heteroskedasticity. Econometrica *48*, 817–838.

61. Kovacic, P., and Jacintho, J.D. (2003). Systemic lupus erythematosus and other autoimmune diseases from endogenous and exogenous agents: unifying theme of oxidative stress. Mini Rev. Med. Chem. *3*, 568–575.

62. Zheng, X., and Sawalha, A.H. (2022). The role of oxidative stress in Epigenetic changes Underlying autoimmunity. Antioxid. Redox Signal. *36*, 423–440. https://doi.org/10.1089/ars.2021.0066.

63. Takahashi, A., Masuda, A., Sun, M., Centonze, V.E., and Herman, B. (2004). Oxidative stress-induced apoptosis is associated with alterations in mitochondrial caspase activity and Bcl-2-dependent alterations in mitochondrial pH (pHm). Brain Res. Bull. *62*, 497–504.

64. Sastre, J., Pallardó, F.V., and Viña, J. (2000). Mitochondrial oxidative stress plays a key role in aging and apoptosis. IUBMB Life *49*, 427–435.

65. Reutelingsperger, C.P., and van Heerde, W.L. (1997). Annexin V, the regulator of phosphatidylserine-catalyzed inflammation and coagulation during apoptosis. Cell. Mol. Life Sci. *53*, 527–532.

66. Sharma, S., and Haldar, C. (2006). Melatonin prevents X-ray irradiation induced oxidative damagein peripheral blood and spleen of the seasonally breeding rodent, Funambulus pennanti during reproductively active phase. Int. J. Radiat. Biol. *82*, 411–419. https://doi.org/10.1080/09553000600774105.

67. Lai, H., and Singh, N.P. (1997). Melatonin and a spin-trap compound block radiofrequency electromagnetic radiation-induced DNA strand breaks in rat brain cells. Bioelectromagnetics *18*, 446–454. https://doi.org/10.1002/(SICI)1521-186X(1997)18:6<446::AID-BEM7>3.0.CO;2-2.

68. Rehman, H., Ali, M., Atif, F., Kaur, M., Bhatia, K., and Raisuddin, S. (2006). The modulatory effect of deltamethrin on antioxidants in mice. Clin. Chim. Acta *369*, 61–65.

69. Barros, S.B., Videla, L.A., Simizu, K., Van Halsema, L., and Junqueira, V.B. (1988). Lindane-induced oxidative stress. II. Time course of changes in hepatic glutathione status. Xenobiotica *18*, 1305–1310.

70. Banerjee, B.D., Seth, V., Bhattacharya, A., Pasha, S.T., and Chakraborty, A.K. (1999). Biochemical effects of some pesticides on lipid peroxidation and free-radical scavengers. Toxicol. Lett. *107*, 33–47.

71. Altuntas, I., Delibas, N., and Sutcu, R. (2002). The effects of organophosphate insecticide methidathion on lipid peroxidation and anti-oxidant enzymes in rat erythrocytes: role of vitamins E and C. Hum. Exp. Toxicol. *21*, 681–685.

72. Junqueira, V.B., Simizu, K., Van Halsema, L., Koch, O.R., Barros, S.B., and Videla, L.A. (1988). Lindane-induced oxidative stress. I. Time course of changes in hepatic microsomal parameters, antioxidant enzymes, lipid peroxidative indices and morphological characteristics. Xenobiotica *18*, 1297–1304.

73. Gultekin, F., Ozturk, M., and Akdogan, M. (2000). The effect of organophosphate insecticide chlorpyrifos-ethyl on lipid peroxidation and antioxidant enzymes (in vitro). Arch. Toxicol. *74*, 533–538.

74. Ahmed, R.S., Suke, S.G., Seth, V., Chakraborti, A., Tripathi, A.K., and Banerjee, B.D. (2008). Protective effects of dietary ginger (Zingiber officinales Rosc.) on lindane-induced oxidative stress in rats. Phytother Res. *22*, 902–906. https://doi.org/10.1002/ptr.2412.

75. Ahmed, R.S., Seth, V., Pasha, S.T., and Banerjee, B.D. (2000). Influence of dietary ginger (Zingiber officinales Rosc) on oxidative stress induced by malathion in rats. Food Chem. Toxicol. *38*, 443–450.

76. Olgun, S., and Misra, H.P. (2006). Pesticides induced oxidative stress in thymocytes. Mol. Cell. Biochem. *290*, 137–144.

77. Oberoi, S., Ahmed, R.S., Suke, S.G., Bhattacharya, S.N., Chakraborti, A., and Banerjee, B.D. (2007). Comparative effect of topical application of lindane and permethrin on oxidative stress parameters in adult scabies patients. Clin. Biochem. *40*, 1321–1324. https://doi.org/10.1016/j.clinbiochem.2007.07.011.

78. Devi, P.U., and Ganasoundari, A. (1999). Modulation of glutathione and antioxidant enzymes by Ocimum sanctum and its role in protection against radiation injury. Indian J. Exp. Biol. *37*, 262–268.

79. Zothansiama, Zosangzuali, M., Lalramdinpuii, M., and Jagetia, G.C. (2017). Impact of radiofrequency radiation on DNA damage and antioxidants in peripheral blood lymphocytes of humans residing in the vicinity of mobile phone base stations. Electromagn. Biol. Med. *36*, 295–305. https://doi.org/10.1080/15368378.2017.1350584.

80. McDonald, J.T., Kim, K., Norris, A.J., Vlashi, E., Phillips, T.M., Lagadec, C., Della Donna, L., Ratikan, J., Szelag, H., Hlatky, L., and McBride, W.H. (2010). Ionizing radiation activates the Nrf2 antioxidant response. Cancer Res. *70*, 8886–8895. https://doi.org/10.1158/0008-5472.CAN-10-0171.

81. Reiter, R.J. (1992). Alterations of the circadian melatonin rhythm by the electromagnetic spectrum: a study in environmental toxicology. Regul. Toxicol. Pharmacol. *15*, 226–244.

82. Reiter, R.J. (1993). Static and extremely low frequency electromagnetic field exposure: reported effects on the circadian production of melatonin. J. Cell. Biochem. *51*, 394–403.

83. Reiter, R.J. (1993). Electromagnetic fields and melatonin production. Biomed. Pharmacother. *47*, 439–444.

84. Reiter, R.J. (1994). Melatonin suppression by static and extremely low frequency electromagnetic fields: relationship to the reported increased incidence of cancer. Rev. Environ. Health *10*, 171–186.

85. Fernie, K.J., Bird, D.M., and Petitclerc, D. (1999). Effects of electromagnetic fields on photophasic circulating melatonin levels in

American kestrels. Environ. Health Perspect. *107*, 901–904.

86. Griefahn, B., Künemund, C., Blaszkewicz, M., Lerchl, A., and Degen, G.H. (2002). Effects of electromagnetic radiation (bright light, extremely low-frequency magnetic fields, infrared radiation) on the circadian rhythm of melatonin synthesis, rectal temperature, and heart rate. Ind. Health *40*, 320–327.

87. Jarupat, S., Kawabata, A., Tokura, H., and Borkiewicz, A. (2003). Effects of the 1900 MHz electromagnetic field emitted from cellular phone on nocturnal melatonin secretion. J. Physiol. Anthropol. Appl. Human Sci. *22*, 61–63.

88. (2005). [Melatonin in the environmental medicine diagnosis in connection with electromagnetic fields: statement of the commission "Methods and Quality Assurance in Environmental Medicine"]. Bundesgesundheitsblatt - Gesundheitsforsch. - Gesundheitsschutz *48*, 1406–1408.

89. Sukhotina, I., Streckert, J.R., Bitz, A.K., Hansen, V.W., and Lerchl, A. (2006). 1800 MHz electromagnetic field effects on melatonin release from isolated pineal glands {X - NONTHERMAL did not suppress melatonin. J. Pineal Res. *40*, 86–91. https://doi.org/10.1111/j.1600-079X.2005.00284.x.

90. Rapoport, S.I., and Breus, T.K. (2011). [Melatonin as a most important factor of natural electromagnetic fields impacting patients with hypertensive disease and coronary heart disease. Part 1]. Klin. Med. (Mosc.) *89*, 9–14.

91. Dyche, J., Anch, A.M., Fogler, K.A.J., Barnett, D.W., and Thomas, C. (2012). Effects of power frequency electromagnetic fields on melatonin and sleep in the rat. Emerg. Health Threats J. *5*, 10904. https://doi.org/10.3402/ehtj.v5i0.10904 EHTJ-5-10904.

92. Qin, F., Zhang, J., Cao, H., Yi, C., Li, J.X., Nie, J., Chen, L.L., Wang, J., and Tong, J. (2012). Effects of 1800-MHz radiofrequency fields on circadian rhythm of plasma melatonin and testosterone in male rats. J. Toxicol. Environ. Health *75*, 1120–1128. https://doi.org/10.1080/15287394.2012.699846.

93. Halgamuge, M.N. (2013). Critical time delay of the pineal melatonin rhythm in humans due to weak electromagnetic exposure. Indian J. Biochem. Biophys. *50*, 259–265.

94. Halgamuge, M.N. (2013). Pineal melatonin level disruption in humans due to electromagnetic fields and ICNIRP limits. Radiat. Prot. Dosimetry *154*, 405–416. https://doi.org/10.1093/rpd/ncs255.

95. Kim, B.C., Shon, B.S., Ryoo, Y.W., Kim, S.P., and Lee, K.S. (2001). Melatonin reduces X-ray irradiation-induced oxidative damages in cultured human skin fibroblasts. J. Dermatol. Sci. *26*, 194–200.

96. Koc, M., Taysi, S., Buyukokuroglu, M.E., and Bakan, N. (2003). Melatonin protects rat liver against irradiation-induced oxidative injury. J. Radiat. Res. *44*, 211–215.

97. Koc, M., Taysi, S., Emin Buyukokuroglu, M., and Bakan, N. (2003). The effect of melatonin against oxidative damage during total-body irradiation in rats. Radiat. Res. *160*, 251–255.

98. Sener, G., Jahovic, N., Tosun, O., Atasoy, B.M., and Yeğen, B.C. (2003). Melatonin ameliorates ionizing radiation-induced oxidative organ damage in rats. Life Sci. *74*, 563–572.

99. Taysi, S., Koc, M., Büyükokuroğlu, M.E., Altinkaynak, K., and Sahin, Y.N. (2003). Melatonin reduces lipid peroxidation and nitric oxide during irradiation-induced oxidative injury in the rat liver. J. Pineal Res. *34*, 173–177.

100. Bhatia, A.L., and Manda, K. (2004). Study on pre-treatment of melatonin against radiation-induced oxidative stress in mice. Environ. Toxicol. Pharmacol. *18*, 13–20. https://doi.org/10.1016/j.etap.2004.05.005.

101. Sener, G., Atasoy, B.M., Ersoy, Y., Arbak, S., Sengöz, M., and Yeğen, B.C. (2004). Melatonin protects against ionizing radiation-induced oxidative damage in corpus cavernosum and urinary bladder in rats. J. Pineal Res. *37*, 241–246.

102. Yilmaz, S., and Yilmaz, E. (2006). Effects of melatonin and vitamin E on oxidative-antioxidative status in rats exposed to irradiation. Toxicology *222*, 1–7. https://doi.org/10.1016/j.tox.2006.02.008.

103. El-Missiry, M.A., Fayed, T.A., El-Sawy, M.R., and El-Sayed, A.A. (2007). Ameliorative effect of melatonin against gamma-irradiation-induced oxidative stress and tissue injury. Ecotoxicol. Environ. Saf. *66*, 278–286. https://doi.org/10.1016/j.ecoenv.2006.03.008.

104. Guney, Y., Hicsonmez, A., Uluoglu, C., Guney, H.Z., Ozel Turkcu, U., Take, G., Yucel, B., Caglar, G., Bilgihan, A., Erdogan, D., et al. (2007). Melatonin prevents inflammation and oxidative stress caused by abdominopelvic and total body irradiation of rat small intestine. Braz. J. Med. Biol. Res. *40*, 1305–1314.

105. Manda, K., Anzai, K., Kumari, S., and Bhatia, A.L. (2007). Melatonin attenuates radiation-induced learning deficit and brain oxidative stress in mice. Acta Neurobiol. Exp. *67*, 63–70.

106. Manda, K., Ueno, M., and Anzai, K. (2008). Melatonin mitigates oxidative damage and apoptosis in mouse cerebellum induced by high-LET 56Fe particle irradiation. J. Pineal Res. *44*, 189–196. https://doi.org/10.1111/j.1600-079X.2007.00507.x.

107. Sokolovic, D., Djindjic, B., Nikolic, J., Bjelakovic, G., Pavlovic, D., Kocic, G., Krstic, D., Cvetkovic, T., and Pavlovic, V. (2008). Melatonin reduces oxidative stress induced by chronic exposure of microwave radiation from mobile phones in rat brain. J. Radiat. Res. *49*, 579–586.

108. Taysi, S., Memisogullari, R., Koc, M., Yazici, A.T., Aslankurt, M., Gumustekin, K., Al, B., Ozabacigil, F., Yilmaz, A., and Tahsin Ozder, H. (2008). Melatonin reduces oxidative stress in the rat lens due to radiation-induced oxidative injury. Int. J. Radiat. Biol. *84*, 803–808. https://doi.org/10.1080/09553000802390932.

109. Naziroğlu, M., Tokat, S., and Demirci, S. (2012). Role of melatonin on electromagnetic radiation-induced oxidative stress and Ca2+ signaling molecular pathways in breast cancer. J. Recept. Signal Transduct. Res. *32*, 290–297. https://doi.org/10.3109/10799893.2012.737002.

110. Goswami, S., Sharma, S., and Haldar, C. (2013). The oxidative damages caused by ultraviolet radiation type C (UVC) to a tropical rodent Funambulus pennanti: role of melatonin. J. Photochem. Photobiol., B *125*, 19–25. https://doi.org/10.1016/j.jphotobiol.2013.04.008.

111. Jang, S.S., Kim, H.G., Lee, J.S., Han, J.M., Park, H.J., Huh, G.J., and Son, C.G. (2013). Melatonin reduces X-ray radiation-induced lung injury in mice by modulating oxidative stress and cytokine expression. Int. J. Radiat. Biol. *89*, 97–105. https://doi.org/10.3109/09553002.2013.734943.

112. Shirazi, A., Mihandoost, E., Mohseni, M., Ghazi-Khansari, M., and Rabie Mahdavi, S. (2013). Radio-protective effects of melatonin against irradiation-induced oxidative damage in rat peripheral blood. Phys. Med. *29*, 65–74. https://doi.org/10.1016/j.ejmp.2011.11.007.

113. Argun, M., Tök, L., Uğuz, A.C., Çelik, Ö., Tök, Ö.Y., and Naziroğlu, M. (2014). Melatonin and amfenac modulate calcium entry, apoptosis, and oxidative stress in ARPE-19 cell culture exposed to blue light irradiation (405 nm). Eye *28*, 752–760. https://doi.org/10.1038/eye.2014.50.

114. Goswami, S., and Haldar, C. (2014). UVB irradiation severely induces systemic tissue injury by augmenting oxidative load in a tropical rodent: efficacy of melatonin as an antioxidant. J. Photochem. Photobiol., B *141*, 84–92. https://doi.org/10.1016/j.jphotobiol.2014.08.027.

115. Meena, R., Kumari, K., Kumar, J., Rajamani, P., Verma, H.N., and Kesari, K.K. (2014). Therapeutic approaches of melatonin in microwave radiations-induced oxidative stress-mediated toxicity on male fertility pattern of Wistar rats. Electromagn. Biol. Med. *33*, 81–91. https://doi.org/10.3109/15368378.2013.781035.

116. Pablos, M.I., Reiter, R.J., Chuang, J.I., Ortiz, G.G., Guerrero, J.M., Sewerynek, E., Agapito, M.T., Melchiorri, D., Lawrence, R., and Deneke, S.M. (1997). Acutely administered melatonin reduces oxidative damage in lung and brain induced by hyperbaric oxygen. J. Appl. Physiol. *83*, 354–358.

117. Morishima, I., Matsui, H., Mukawa, H., Hayashi, K., Toki, Y., Okumura, K., Ito, T., and Hayakawa, T. (1998). Melatonin, a pineal

hormone with antioxidant property, protects against adriamycin cardiomyopathy in rats. Life Sci. *63*, 511–521.

118. Chen, S.T., and Chuang, J.I. (1999). The antioxidant melatonin reduces cortical neuronal death after intrastriatal injection of kainate in the rat. Exp. Brain Res. *124*, 241–247.

119. Romero, M.P., Osuna, C., García-Pergañeda, A., Carrillo-Vico, A., and Guerrero, J.M. (1999). The pineal secretory product melatonin reduces hydrogen peroxide-induced DNA damage in U-937 cells. J. Pineal Res. *26*, 227–235.

120. Tesoriere, L., D'Arpa, D., Conti, S., Giaccone, V., Pintaudi, A.M., and Livrea, M.A. (1999). Melatonin protects human red blood cells from oxidative hemolysis: new insights into the radical-scavenging activity. J. Pineal Res. *27*, 95–105.

121. Wakatsuki, A., Okatani, Y., Izumiya, C., and Ikenoue, N. (1999). Melatonin protects against ischemia and reperfusion-induced oxidative lipid and DNA damage in fetal rat brain. J. Pineal Res. *26*, 147–152.

122. Cabrera, J., Reiter, R.J., Tan, D.X., Qi, W., Sainz, R.M., Mayo, J.C., Garcia, J.J., Kim, S.J., and El-Sokkary, G. (2000). Melatonin reduces oxidative neurotoxicity due to quinolinic acid: in vitro and in vivo findings. Neuropharmacology *39*, 507–514.

123. Karbownik, M., Reiter, R.J., Garcia, J.J., and Tan, D. (2000). Melatonin reduces phenylhydrazine-induced oxidative damage to cellular membranes: evidence for the involvement of iron. Int. J. Biochem. Cell Biol. *32*, 1045–1054.

124. Karbownik, M., Reiter, R.J., Garcia, J.J., Tan, D.X., Qi, W., and Manchester, L.C. (2000). Melatonin reduces rat hepatic macromolecular damage due to oxidative stress caused by delta-aminolevulinic acid. Biochim. Biophys. Acta *1523*, 140–146.

125. Nava, M., Romero, F., Quiroz, Y., Parra, G., Bonet, L., and Rodríguez-Iturbe, B. (2000). Melatonin attenuates acute renal failure and oxidative stress induced by mercuric chloride in rats. Am. J. Physiol. Renal Physiol. *279*, F910–F918.

126. Shifow, A.A., Kumar, K.V., Naidu, M.U., and Ratnakar, K.S. (2000). Melatonin, a pineal hormone with antioxidant property, protects against gentamicin-induced nephrotoxicity in rats. Nephron *85*, 167–174.

127. Hara, M., Yoshida, M., Nishijima, H., Yokosuka, M., Iigo, M., Ohtani-Kaneko, R., Shimada, A., Hasegawa, T., Akama, Y., and Hirata, K. (2001). Melatonin, a pineal secretory product with antioxidant properties, protects against cisplatin-induced nephrotoxicity in rats. J. Pineal Res. *30*, 129–138.

128. Karbownik, M., Reiter, R.J., Burkhardt, S., Gitto, E., Tan, D.X., and Lewiński, A. (2001). Melatonin attenuates estradiol-induced oxidative damage to DNA: relevance for cancer prevention. Exp. Biol. Med. *226*, 707–712.

129. Meki, A.R., and Hussein, A.A. (2001). Melatonin reduces oxidative stress induced by ochratoxin A in rat liver and kidney. Comp. Biochem. Physiol. C Toxicol. Pharmacol. *130*, 305–313.

130. Tomás-Zapico, C., Martínez-Fraga, J., Rodríguez-Colunga, M.J., Tolivia, D., Hardeland, R., and Coto-Montes, A. (2002). Melatonin protects against delta-aminolevulinic acid-induced oxidative damage in male Syrian hamster Harderian glands. Int. J. Biochem. Cell Biol. *34*, 544–553.

131. Rosales-Corral, S., Tan, D.X., Reiter, R.J., Valdivia-Velázquez, M., Martínez-Barboza, G., Acosta-Martínez, J.P., and Ortiz, G.G. (2003). Orally administered melatonin reduces oxidative stress and proinflammatory cytokines induced by amyloid-beta peptide in rat brain: a comparative, in vivo study versus vitamin C and E. J. Pineal Res. *35*, 80–84.

132. Bandyopadhyay, D., Ghosh, G., Bandyopadhyay, A., and Reiter, R.J. (2004). Melatonin protects against piroxicam-induced gastric ulceration. J. Pineal Res. *36*, 195–203.

133. Bruck, R., Aeed, H., Avni, Y., Shirin, H., Matas, Z., Shahmurov, M., Avinoach, I., Zozulya, G., Weizman, N., and Hochman, A. (2004). Melatonin inhibits nuclear factor kappa B activation and oxidative stress and protects against thioacetamide induced liver damage in rats. J. Hepatol. *40*, 86–93.

134. Thomas, B., and Mohanakumar, K.P. (2004). Melatonin protects against oxidative stress caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the mouse nigrostriatum. J. Pineal Res. *36*, 25–32.

135. Esparza, J.L., Gómez, M., Rosa Nogués, M., Paternain, J.L., Mallol, J., and Domingo, J.L. (2005). Melatonin reduces oxidative stress and increases gene expression in the cerebral cortex and cerebellum of aluminum-exposed rats. J. Pineal Res. *39*, 129–136.

136. Tunali, T., Sener, G., Yarat, A., and Emekli, N. (2005). Melatonin reduces oxidative damage to skin and normalizes blood coagulation in a rat model of thermal injury. Life Sci. *76*, 1259–1265. https://doi.org/10.1016/j.lfs.2004.08.024.

137. Nogués, M.R., Giralt, M., Romeu, M., Mulero, M., Sánchez-Martos, V., Rodríguez, E., Acuña-Castroviejo, D., and Mallol, J. (2006). Melatonin reduces oxidative stress in erythrocytes and plasma of senescence-accelerated mice. J. Pineal Res. *41*, 142–149. https://doi.org/10.1111/j.1600-079X.2006.00344.x.

138. Sener, G., Sert, G., Ozer Sehirli, A., Arbak, S., Gedik, N., and Ayanoğlu-Dülger, G. (2006). Melatonin protects against pressure ulcer-induced oxidative injury of the skin and remote organs in rats. J. Pineal Res. *40*, 280–287. https://doi.org/10.1111/j.1600-079X.2005.00313.x.

139. Sadir, S., Deveci, S., Korkmaz, A., and Oter, S. (2007). Alpha-tocopherol, beta-carotene and melatonin administration protects cyclophosphamide-induced oxidative damage to bladder tissue in rats. Cell Biochem. Funct. *25*, 521–526. https://doi.org/10.1002/cbf.1347.

140. Saravanan, K.S., Sindhu, K.M., and Mohanakumar, K.P. (2007). Melatonin protects against rotenone-induced oxidative stress in a hemiparkinsonian rat model. J. Pineal Res. *42*, 247–253. https://doi.org/10.1111/j.1600-079X.2006.00412.x.

141. Omurtag, G.Z., Tozan, A., Sehirli, A.O., and Sener, G. (2008). Melatonin protects against endosulfan-induced oxidative tissue damage in rats. J. Pineal Res. *44*, 432–438. https://doi.org/10.1111/j.1600-079X.2007.00546.x.

142. Reiter, R.J., Korkmaz, A., Paredes, S.D., Manchester, L.C., and Tan, D.X. (2008). Melatonin reduces oxidative/nitrosative stress due to drugs, toxins, metals, and herbicides. Neuroendocrinol. Lett. *29*, 609–613.

143. Mahieu, S., Contini, M.d.C., González, M., and Millen, N. (2009). Melatonin reduces oxidative damage induced by aluminium in rat kidney. Toxicol. Lett. *190*, 9–15. https://doi.org/10.1016/j.toxlet.2009.06.852.

144. Maity, P., Bindu, S., Dey, S., Goyal, M., Alam, A., Pal, C., Reiter, R., and Bandyopadhyay, U. (2009). Melatonin reduces indomethacin-induced gastric mucosal cell apoptosis by preventing mitochondrial oxidative stress and the activation of mitochondrial pathway of apoptosis. J. Pineal Res. *46*, 314–323. https://doi.org/10.1111/j.1600-079X.2009.00663.x.

145. Sönmez, M.F., Narin, F., and Balcioğlu, E. (2009). Melatonin and vitamin C attenuates alcohol-induced oxidative stress in aorta. Basic Clin. Pharmacol. Toxicol. *105*, 410–415. https://doi.org/10.1111/j.1742-7843.2009.00469.x.

146. Fuentes-Broto, L., Miana-Mena, F.J., Piedrafita, E., Berzosa, C., Martínez-Ballarín, E., García-Gil, F.A., Reiter, R.J., and García, J.J. (2010). Melatonin protects against taurolithocholic-induced oxidative stress in rat liver. J. Cell. Biochem. *110*, 1219–1225. https://doi.org/10.1002/jcb.22636.

147. Xu, S.C., He, M.D., Zhong, M., Zhang, Y.W., Wang, Y., Yang, L., Yang, J., Yu, Z.P., and Zhou, Z. (2010). Melatonin protects against Nickel-induced neurotoxicity in vitro by reducing oxidative stress and maintaining mitochondrial function. J. Pineal Res. *49*, 86–94. https://doi.org/10.1111/j.1600-079X.2010.00770.x.

148. Ortiz, G.G., Pacheco-Moisés, F.P., Gómez-Rodríguez, V.M., González-Renovato, E.D., Torres-Sánchez, E.D., and Ramírez-Anguiano, A.C. (2013). Fish oil, melatonin and vitamin E attenuates midbrain cyclooxygenase-2 activity and oxidative stress after the administration of 1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine. Metab. Brain Dis. *28*, 705–709. https://doi.org/10.1007/s11011-013-9416-0.

149. Sharma, A.K., Mehta, A.K., Rathor, N., Chalawadi Hanumantappa, M.K., Khanna, N., and Bhattacharya, S.K. (2013). Melatonin attenuates cognitive dysfunction and reduces neural oxidative stress induced by phosphamidon. Fundam. Clin. Pharmacol. *27*, 146–151. https://doi.org/10.1111/j.1472-8206.2011.00977.x.

150. Suwanjang, W., Abramov, A.Y., Govitrapong, P., and Chetsawang, B. (2013). Melatonin attenuates dexamethasone toxicity-induced oxidative stress, calpain and caspase activation in human neuroblastoma SH-SY5Y cells. J. Steroid Biochem. Mol. Biol. *138*, 116–122. https://doi.org/10.1016/j.jsbmb.2013.04.008.

151. El-Missiry, M.A., Othman, A.I., Al-Abdan, M.A., and El-Sayed, A.A. (2014). Melatonin ameliorates oxidative stress, modulates death receptor pathway proteins, and protects the rat cerebrum against bisphenol-A-induced apoptosis. J. Neurol. Sci. *347*, 251–256. https://doi.org/10.1016/j.jns.2014.10.009.

152. Sun, M., Xu, P.P., Ren, Y., Li, Y.F., Zhong, Y.F., and Yan, H. (2007). [Protective effect of melatonin on oxidative damage by deltamethrin in rat brain]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi *25*, 155–158.

153. Buyukokuroglu, M.E., Cemek, M., Yurumez, Y., Yavuz, Y., and Aslan, A. (2008). Antioxidative role of melatonin in organophosphate toxicity in rats. Cell Biol. Toxicol. *24*, 151–158. https://doi.org/10.1007/s10565-007-9024-z.

154. Gultekin, F., Patat, S., Akca, H., Akdogan, M., and Altuntas, I. (2006). Melatonin can suppress the cytotoxic effects of chlorpyrifos on human hepG2 cell lines. Hum. Exp. Toxicol. *25*, 47–55.

155. Umosen, A.J., Ambali, S.F., Ayo, J.O., Mohammed, B., and Uchendu, C. (2012). Alleviating effects of melatonin on oxidative changes in the testes and pituitary glands evoked by subacute chlorpyrifos administration in Wistar rats. Asian Pac. J. Trop. Biomed. *2*, 645–650. https://doi.org/10.1016/S2221-1691(12)60113-0 apjtb-02-08-645.

156. Belpomme, D., Campagnac, C., and Irigaray, P. (2015). Reliable disease biomarkers characterizing and identifying electrohypersensitivity and multiple chemical sensitivity as two etiopathogenic aspects of a unique pathological disorder. Rev. Environ. Health *30*, 251–271. https://doi.org/10.1515/reveh-2015-0027.

157. Al Kaddissi, S., Legeay, A., Elia, A.C., Gonzalez, P., Camilleri, V., Gilbin, R., and Simon, O. (2012). Effects of uranium on crayfish Procambarus clarkii mitochondria and antioxidants responses after chronic exposure: what have we learned? Ecotoxicol. Environ. Saf. *78*, 218–224. https://doi.org/10.1016/j.ecoenv.2011.11.026.

158. Torbenko, V.P., Bogdanova, I.A., and Gerasimov, A.M. (1983). [Effect of a combined radiation lesion on the enzyme activity of the glutathione redox system of the rat liver]. Biull. Eksp. Biol. Med. *95*, 48–50.

159. Erden, M., and Bor, N.M. (1984). Changes of reduced glutathion, glutathion reductase, and glutathione peroxidase after radiation in Guinea pigs. Biochem. Med. *31*, 217–227.

160. Evans, J.W., Taylor, Y.C., and Brown, J.M. (1984). The role of glutathione and DNA strand break repair in determining the shoulder of the radiation survival curve. Br. J. Cancer Suppl. *6*, 49–53.

161. Boyer, T.D., Vessey, D.A., and Kempner, E. (1986). Radiation inactivation of microsomal glutathione S-transferase. J. Biol. Chem. *261*, 16963–16968.

162. Connor, M.J., and Wheeler, L.A. (1987). Depletion of cutaneous glutathione by ultraviolet radiation. Photochem. Photobiol. *46*, 239–245.

163. Singh, L.R., Uniyal, B.P., Mukherjee, S.K., Sarkar, S.R., and Sharma, S.K. (1987). Effect of whole body gamma-radiation on glutathione reductase of rat tissues. Strahlenther. Onkol. *163*, 337–339.

164. Leus, N.F., Kolomiĭchuk, S.G., and Lishchenko, V.B. (1997). [Activity of glutathione-S-transferase in the blood plasma, liver and crystalline lens tissues as affected by low doses of ionizing radiation and polychromatic light]. Ukr. Biokhim. Zh. *69*, 54–59.

165. Gudz, T.I., Peshkova, E.G., and Goncharenko, E.N. (1982). [Effect of ionizing radiation on glutathione peroxidase activity in rat tissues]. Radiobiologiia *22*, 515–516.

166. Biswas, S.K., and Rahman, I. (2009). Environmental toxicity, redox signaling and lung inflammation: the role of glutathione. Mol. Aspects Med. *30*, 60–76. https://doi.org/10.1016/j.mam.2008.07.001.

167. Cronkite, E.P., Brecher, G., and Chapman, W.H. (1951). Studies on the mechanism of the protective action of glutathione against whole body radiation. Mil. Surg. *109*, 294–307.

168. Edgren, M., and Révész, L. (1985). Glutathione requirement for the rejoining of radiation-induced DNA breaks in misonidazole-treated cells. Int. J. Radiat. Biol. Relat. Stud. Phys. Chem. Med. *48*, 207–212.

169. Fu, Y., Cheng, W.H., Porres, J.M., Ross, D.A., and Lei, X.G. (1999). Knockout of cellular glutathione peroxidase gene renders mice susceptible to diquat-induced oxidative stress. Free Radic. Biol. Med. *27*, 605–611.

170. Hollingworth, R.M., Alstott, R.L., and Litzenberg, R.D. (1973). Glutathione S-aryl transferase in the metabolism of parathion and its analogs. Life Sci. *13*, 191–199.

171. Hayes, J.D., and Pulford, D.J. (1995). The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit. Rev. Biochem. Mol. Biol. *30*, 445–600. https://doi.org/10.3109/10409239509083491.

172. Nakagawa, I., Suzuki, M., Imura, N., and Naganuma, A. (1998). Involvement of oxidative stress in paraquat-induced metallothionein synthesis under glutathione depletion. Free Radic. Biol. Med. *24*, 1390–1395.

173. Nurulain, S.M., Ojha, S., Tekes, K., Shafiullah, M., Kalasz, H., and Adem, A. (2015). Efficacy of N-Acetylcysteine, glutathione, and Ascorbic acid in acute toxicity of Paraoxon to Wistar rats: survival study. Oxid. Med. Cell. Longev. *2015*, 329306. https://doi.org/10.1155/2015/329306.

174. Jernström, B., Morgenstern, R., and Moldéus, P. (1993). Protective role of glutathione, thiols, and analogues in mutagenesis and carcinogenesis. Basic Life Sci. *61*, 137–147.

175. Malmgren, R., Unge, G., Zetterström, O., Theorell, H., and de Wahl, K. (1986). Lowered glutathione-peroxidase activity in asthmatic patients with food and aspirin intolerance. Allergy *41*, 43–45.

176. Mårtensson, J., Steinherz, R., Jain, A., and Meister, A. (1989). Glutathione ester prevents buthionine sulfoximine-induced cataracts and lens epithelial cell damage. Proc. Natl. Acad. Sci. USA. *86*, 8727–8731.

177. Tu, B., Wallin, A., Moldéus, P., and Cotgreave, I. (1995). The cytoprotective roles of ascorbate and glutathione against nitrogen dioxide toxicity in human endothelial cells. Toxicology *98*, 125–136.

178. Zhang, Z.J., Hao, K., Shi, R., Zhao, G., Jiang, G.X., Song, Y., Xu, X., and Ma, J. (2011). Glutathione S-transferase M1 (GSTM1) and glutathione S-transferase T1 (GSTT1) null polymorphisms, smoking, and their interaction in oral cancer: a HuGE review and meta-analysis. Am. J. Epidemiol. *173*, 847–857. https://doi.org/10.1093/aje/kwq480.

179. Matic, M.G., Coric, V.M., Savic-Radojevic, A.R., Bulat, P.V., Pljesa-Ercegovac, M.S., Dragicevic, D.P., Djukic, T.I., Simic, T.P., and Pekmezovic, T.D. (2014). Does occupational exposure to solvents and pesticides in association with glutathione S-transferase A1, M1, P1, and T1 polymorphisms increase the risk of bladder cancer? The Belgrade case-control study. PLoS One *9*, e99448. https://doi.org/10.1371/journal.pone.0099448 PONE-D-13-51090.

180. Oleinick, N.L., Xue, L.Y., Friedman, L.R., Donahue, L.L., and Biaglow, J.E. (1988). Inhibition of radiation-induced DNA-protein cross-link repair by glutathione depletion with L-buthionine sulfoximine. NCI (Natl. Cancer Inst.) Monogr. 225–229.

181. Bui, L., Nguyen, E., Dinkeloo, E., Ritchie, J., and Golomb, B.A. (2020). Nuclear and mitochondrial genetics Together determine gulf war illness severity and symptom Profile. Gulf War Illness 2020 State of the Science

Virtual Conference 8/18/2020. https://va-eerc-ees.adobeconnect.com/_a1089657440/plixyd1089657440rh1089657444ht/?OWASP_CSRFTOKEN=1089657487e1827022744e1089657442d1089657447d1032270316e1089657441df1089657445a1089657442b1089657441c1089657442abb1089657425c1089651687a108965746f1089657447eb1089657442ce1089657448b1089657449cba1089657444&proto=true.

182. De Luca, C., Scordo, M.G., Cesareo, E., Pastore, S., Mariani, S., Maiani, G., Stancato, A., Loreti, B., Valacchi, G., Lubrano, C., et al. (2010). Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. Toxicol. Appl. Pharmacol. *248*, 285–292. https://doi.org/10.1016/j.taap.2010.04.017.

183. Feland, B., and Smith, J.T. (1972). Malathion intoxication and mitochondrial damage. J. Agric. Food Chem. *20*, 1274–1275.

184. Shabarchin, E.I., Kruglyakova, K.E., Gendel, L.Y., and Kabanov, V.V. (1979). Influence of metaphos on the structuro-functional organization of mitochondrial membranes. Biol. Bull. Acad. Sci. USSR *6*, 788–793.

185. Pardini, R.S., Heidker, J.C., Baker, T.A., and Payne, B. (1980). Toxicology of various pesticides and their decomposition products on mitochondrial electron transport. Arch. Environ. Contam. Toxicol. *9*, 87–97.

186. Zhang, J., Fitsanakis, V.A., Gu, G., Jing, D., Ao, M., Amarnath, V., and Montine, T.J. (2003). Manganese ethylene-bis-dithiocarbamate and selective dopaminergic neurodegeneration in rat: a link through mitochondrial dysfunction. J. Neurochem. *84*, 336–346.

187. Yen, D.H.T., Chan, J.Y.H., Tseng, H.P., Huang, C.I., Lee, C.H., Chan, S.H.H., and Chang, A.Y.W. (2004). Depression of mitochondrial respiratory enzyme activity in rostral ventrolateral medulla during acute mevinphos intoxication in the rat. Shock *21*, 358–363.

188. Chan, J.Y.H., Chan, S.H.H., Dai, K.Y., Cheng, H.L., Chou, J.L.J., and Chang, A.Y.W. (2006). Cholinergic-receptor-independent dysfunction of mitochondrial respiratory chain enzymes, reduced mitochondrial transmembrane potential **and ATP depletion** underlie necrotic cell death induced by the organophosphate poison mevinphos. Neuropharmacology *51*, 1109–1119. https://doi.org/10.1016/j.neuropharm.2006.06.024.

189. Delgado, E.H.B., Streck, E.L., Quevedo, J.L., and Dal-Pizzol, F. (2006). Mitochondrial respiratory dysfunction and oxidative stress after chronic malathion exposure. Neurochem. Res. *31*, 1021–1025. https://doi.org/10.1007/s11064-006-9111-1.

190. Gash, D.M., Rutland, K., Hudson, N.L., Sullivan, P.G., Bing, G., Cass, W.A., Pandya, J.D., Liu, M., Choi, D.Y., Hunter, R.L., et al. (2008). Trichloroethylene: Parkinsonism and complex 1 mitochondrial neurotoxicity. Ann. Neurol. *63*, 184–192. https://doi.org/10.1002/ana.21288.

191. Masoud, A., Kiran, R., and Sandhir, R. (2009). Impaired mitochondrial functions in organophosphate induced delayed neuropathy in rats. Cell. Mol. Neurobiol. *29*, 1245–1255. https://doi.org/10.1007/s10571-009-9420-4.

192. Venkatesh, S., Ramachandran, A., Zachariah, A., and Oommen, A. (2009). Mitochondrial ATP synthase inhibition and nitric oxide are involved in muscle weakness that occurs in acute exposure of rats to monocrotophos. Toxicol. Mech. Methods *19*, 239–245. https://doi.org/10.1080/15376510802455354.

193. Binukumar, B.K., Bal, A., Kandimalla, R., Sunkaria, A., and Gill, K.D. (2010). Mitochondrial energy metabolism impairment and liver dysfunction following chronic exposure to dichlorvos. Toxicology *270*, 77–84. https://doi.org/10.1016/j.tox.2010.01.017.

194. Ranjbar, A., Ghahremani, M.H., Sharifzadeh, M., Golestani, A., Ghazi-Khansari, M., Baeeri, M., and Abdollahi, M. (2010). Protection by pentoxifylline of malathion-induced toxic stress and mitochondrial damage in rat brain. Hum. Exp. Toxicol. *29*, 851–864. https://doi.org/10.1177/0960327110363836.

195. Shafiee, H., Mohammadi, H., Rezayat, S.M., Hosseini, A., Baeeri, M., Hassani, S., Mohammadirad, A., Bayrami, Z., and Abdollahi, M. (2010). Prevention of malathion-induced depletion of cardiac cells mitochondrial energy and free radical damage by a magnetic magnesium-carrying nanoparticle. Toxicol. Mech. Methods *20*, 538–543. https://doi.org/10.3109/15376516.2010.518173.

196. Gupta, G., Chaitanya, R.K., Golla, M., and Karnati, R. (2013). Allethrin toxicity on human corneal epithelial cells involves mitochondrial pathway mediated apoptosis. Toxicol. Vitro *27*, 2242–2248. https://doi.org/10.1016/j.tiv.2013.09.011.

197. Basha, P.M., and Poojary, A. (2014). Mitochondrial dysfunction in aging rat brain regions upon chlorpyrifos toxicity and cold stress: an interactive study. Cell. Mol. Neurobiol. *34*, 737–756. https://doi.org/10.1007/s10571-014-0056-7.

198. Karami-Mohajeri, S., Hadian, M.R., Fouladdel, S., Azizi, E., Ghahramani, M.H., Hosseini, R., and Abdollahi, M. (2014). Mechanisms of muscular electrophysiological and mitochondrial dysfunction following exposure to malathion, an organophosphorus pesticide. Hum. Exp. Toxicol. *33*, 251–263. https://doi.org/10.1177/0960327113493300.

199. Salama, M., El-Morsy, D., El-Gamal, M., Shabka, O., and Mohamed, W.M. (2014). Mitochondrial complex I inhibition as a possible mechanism of chlorpyrifos induced neurotoxicity. Ann. Neurosci. *21*, 85–89. https://doi.org/10.5214/ans.0972.7531.210303 210303.

200. Agrawal, S., Singh, A., Tripathi, P., Mishra, M., Singh, P.K., and Singh, M.P. (2015). Cypermethrin-induced nigrostriatal dopaminergic neurodegeneration alters the mitochondrial function: a proteomics study. Mol. Neurobiol. *51*, 448–465. https://doi.org/10.1007/s12035-014-8696-7.

201. Liu, Q., Wang, Q., Xu, C., Shao, W., Zhang, C., Liu, H., Jiang, Z., and Gu, A. (2017). Organochloride pesticides impaired mitochondrial function in hepatocytes and aggravated disorders of fatty acid metabolism. Sci. Rep. *7*, 46339. https://doi.org/10.1038/srep46339.

202. Binukumar, B.K., Bal, A., Kandimalla, R.J.L., and Gill, K.D. (2010). Nigrostriatal neuronal death following chronic dichlorvos exposure: crosstalk between mitochondrial impairments, alpha synuclein aggregation, oxidative damage and behavioral changes. Mol. Brain *3*, 35. https://doi.org/10.1186/1756-6606-3-35.

203. Wani, W.Y., Gudup, S., Sunkaria, A., Bal, A., Singh, P.P., Kandimalla, R.J.L., Sharma, D.R., and Gill, K.D. (2011). Protective efficacy of mitochondrial targeted antioxidant MitoQ against dichlorvos induced oxidative stress and cell death in rat brain. Neuropharmacology *61*, 1193–1201. https://doi.org/10.1016/j.neuropharm.2011.07.008.

204. Rodriguez-Lafrasse, C., Alphonse, G., Aloy, M.T., Ardail, D., Gérard, J.P., Louisot, P., and Rousson, R. (2002). Increasing endogenous ceramide using inhibitors of sphingolipid metabolism maximizes ionizing radiation-induced mitochondrial injury and apoptotic cell killing. Int. J. Cancer *101*, 589–598. https://doi.org/10.1002/ijc.10652.

205. Shonai, T., Adachi, M., Sakata, K., Takekawa, M., Endo, T., Imai, K., and Hareyama, M. (2002). MEK/ERK pathway protects ionizing radiation-induced loss of mitochondrial membrane potential and cell death in lymphocytic leukemia cells. Cell Death Differ. *9*, 963–971. https://doi.org/10.1038/sj.cdd.4401050.

206. Goel, H.C., Gupta, D., Gupta, S., Garg, A.P., and Bala, M. (2005). Protection of mitochondrial system by Hippophae rhamnoides L. against radiation-induced oxidative damage in mice. J. Pharm. Pharmacol. *57*, 135–143.

207. Mishmar, D., Ruiz-Pesini, E., Mondragon-Palomino, M., Procaccio, V., Gaut, B., and Wallace, D.C. (2006). Adaptive selection of mitochondrial complex I subunits during primate radiation. Gene *378*, 11–18.

208. Birket, M.J., and Birch-Machin, M.A. (2007). Ultraviolet radiation exposure accelerates the accumulation of the aging-dependent T414G mitochondrial DNA mutation in human skin. Aging Cell *6*, 557–564. https://doi.org/10.1111/j.1474-9726.2007.00310.x.

209. Lee, J.H., Kim, S.Y., Kil, I.S., and Park, J.W. (2007). Regulation of ionizing radiation-induced apoptosis by mitochondrial NADP+-dependent isocitrate dehydrogenase. J. Biol. Chem. *282*, 13385–13394. https://doi.org/10.1074/jbc.M700303200.

210. Xu, S., Zhou, Z., Zhang, L., Yu, Z., Zhang, W., Wang, Y., Wang, X., Li, M., Chen, Y., Chen, C., et al. (2010). Exposure to 1800 MHz radiofrequency radiation induces oxidative damage to mitochondrial DNA in primary cultured neurons. Brain Res. *1311*, 189–196. https://doi.org/10.1016/j.brainres.2009.10.062.

211. Calabrò, E., Condello, S., Currò, M., Ferlazzo, N., Vecchio, M., Caccamo, D., Magazù, S., and Ientile, R. (2013). 50 Hz electromagnetic field produced changes in FTIR spectroscopy associated with mitochondrial transmembrane potential reduction in neuronal-like SH-SY5Y cells. Oxid. Med. Cell. Longev. *2013*, 414393. https://doi.org/10.1155/2013/414393.

212. Shaki, F., and Pourahmad, J. (2013). Mitochondrial toxicity of depleted uranium: protection by Beta-glucan. Iran. J. Pharm. Res. (IJPR) *12*, 131–140.

213. Shaki, F., Hosseini, M.J., Ghazi-Khansari, M., and Pourahmad, J. (2013). Depleted uranium induces disruption of energy homeostasis and oxidative stress in isolated rat brain mitochondria. Metallomics *5*, 736–744. https://doi.org/10.1039/c3mt00019b.

214. Shaki, F., Hosseini, M.J., Ghazi-Khansari, M., and Pourahmad, J. (2012). Toxicity of depleted uranium on isolated rat kidney mitochondria. Biochim. Biophys. Acta *1820*, 1940–1950. https://doi.org/10.1016/j.bbagen.2012.08.015.

215. Kovacic, P. (2003). Mechanism of organophosphates (nerve gases and pesticides) and antidotes: electron transfer and oxidative stress. Curr. Med. Chem. *10*, 2705–2709.

216. Abdollahi, M., Ranjbar, A., Shadnia, S., Nikfar, S., and Rezaie, A. (2004). Pesticides and oxidative stress: a review. Med. Sci. Monit. *10*.

217. Singh, C., Ahmad, I., and Kumar, A. (2007). Pesticides and metals induced Parkinson's disease: involvement of free radicals and oxidative stress. Cell. Mol. Biol. *53*, 19–28.

218. Slaninova, A., Smutna, M., Modra, H., and Svobodova, Z. (2009). A review: oxidative stress in fish induced by pesticides. Neuroendocrinol. Lett. *30* (*Suppl 1*), 2–12.

219. Astiz, M., de Alaniz, M.J.T., and Marra, C.A. (2012). The oxidative damage and inflammation caused by pesticides are reverted by lipoic acid in rat brain. Neurochem. Int. *61*, 1231–1241. https://doi.org/10.1016/j.neuint.2012.09.003.

220. Lu, X.T., Ma, Y., Wang, C., Zhang, X.F., Jin, D.Q., and Huang, C.J. (2012). Cytotoxicity and DNA damage of five organophosphorus pesticides mediated by oxidative stress in PC12 cells and protection by vitamin E. J. Environ. Sci. Health. B *47*, 445–454. https://doi.org/10.1080/03601234.2012.663312.

221. Wafa, T., Nadia, K., Amel, N., Ikbal, C., Insaf, T., Asma, K., Hedi, M.A., and Mohamed, H. (2013). Oxidative stress, hematological and biochemical alterations in farmers exposed to pesticides. J. Environ. Sci. Health. B *48*, 1058–1069. https://doi.org/10.1080/03601234.2013.824285.

222. Ojha, A., and Srivastava, N. (2014). In vitro studies on organophosphate pesticides induced oxidative DNA damage in rat lymphocytes. Mutat. Res. Genet. Toxicol. Environ. Mutagen. *761*, 10–17. https://doi.org/10.1016/j.mrgentox.2014.01.007.

223. Ma, Z.C., Hong, Q., Wang, Y.G., Tan, H.L., Xiao, C.R., Liang, Q.D., Wang, D.G., and Gao, Y. (2011). Ferulic acid protects lymphocytes from radiation-predisposed oxidative stress through extracellular regulated kinase. Int. J. Radiat. Biol. *87*, 130–140. https://doi.org/10.3109/09553002.2011.523510.

224. Avci, B., Akar, A., Bilgici, B., and Tunçel, Ö.K. (2012). Oxidative stress induced by 1.8 GHz radio frequency electromagnetic radiation and effects of garlic extract in rats. Int. J. Radiat. Biol. *88*, 799–805. https://doi.org/10.3109/09553002.2012.711504.

225. Sahin, D., Ozgur, E., Guler, G., Tomruk, A., Unlu, I., Sepici-Dinçel, A., and Seyhan, N. (2016). The 2100MHz radiofrequency radiation of a 3G-mobile phone and the DNA oxidative damage in brain. J. Chem. Neuroanat. *75*, 94–98. https://doi.org/10.1016/j.jchemneu.2016.01.002.

226. Yakymenko, I., Tsybulin, O., Sidorik, E., Henshel, D., Kyrylenko, O., and Kyrylenko, S. (2016). Oxidative mechanisms of biological activity of low-intensity radiofrequency radiation. Electromagn. Biol. Med. *35*, 186–202. https://doi.org/10.3109/15368378.2015.1043557.

227. Copeland, E.S. (1969). Production of free radicals in reduced glutathione and penicillamine by thermal hydrogen atoms and X-radiation. Int. J. Radiat. Biol. Relat. Stud. Phys. Chem. Med. *16*, 113–120.

228. Jurkiewicz, B.A., Bissett, D.L., and Buettner, G.R. (1995). Effect of topically applied tocopherol on ultraviolet radiation-mediated free radical damage in skin. J. Invest. Dermatol. *104*, 484–488.

229. Agrawal, A., Chandra, D., and Kale, R.K. (2001). Radiation induced oxidative stress: II studies in liver as a distant organ of tumor bearing mice. Mol. Cell. Biochem. *224*, 9–17.

230. Benderitter, M., Vincent-Genod, L., Pouget, J.P., and Voisin, P. (2003). The cell membrane as a biosensor of oxidative stress induced by radiation exposure: a multiparameter investigation. Radiat. Res. *159*, 471–483.

231. Ogawa, Y., Kobayashi, T., Nishioka, A., Kariya, S., Hamasato, S., Seguchi, H., and Yoshida, S. (2003). Radiation-induced reactive oxygen species formation prior to oxidative DNA damage in human peripheral T cells. Int. J. Mol. Med. *11*, 149–152.

232. Ogawa, Y., Kobayashi, T., Nishioka, A., Kariya, S., Hamasato, S., Seguchi, H., and Yoshida, S. (2003). Radiation-induced oxidative DNA damage, 8-oxoguanine, in human peripheral T cells. Int. J. Mol. Med. *11*, 27–32.

233. Tulard, A., Hoffschir, F., de Boisferon, F.H., Luccioni, C., and Bravard, A. (2003). Persistent oxidative stress after ionizing radiation is involved in inherited radiosensitivity. Free Radic. Biol. Med. *35*, 68–77.

234. Shi, S., Wang, G., Wang, Y., Zhang, L., and Zhang, L. (2005). Protective effect of nitric oxide against oxidative stress under ultraviolet-B radiation. Nitric Oxide *13*, 1–9.

235. Wan, X.S., Bloch, P., Ware, J.H., Zhou, Z., Donahue, J.J., Guan, J., Stewart, J., and Kennedy, A.R. (2005). Detection of oxidative stress induced by low- and high-linear energy transfer radiation in cultured human epithelial cells. Radiat. Res. *163*, 364–368.

236. Lantow, M., Schuderer, J., Hartwig, C., and Simkó, M. (2006). XFree radical release and HSP70 expression in two human immune-relevant cell lines after exposure to 1800 MHz radiofrequency radiation. Radiat. Res. *165*, 88–94.

237. Mulero, M., Romeu, M., Giralt, M., Folch, J., Nogués, M.R., Fortuño, A., Sureda, F.X., Linares, V., Cabré, M., Paternáin, J.L., and Mallol, J. (2006). Oxidative stress-related markers and langerhans cells in a hairless rat model exposed to UV radiation. J. Toxicol. Environ. Health *69*, 1371–1385.

238. Sener, G., Kabasakal, L., Atasoy, B.M., Erzik, C., Velioğlu-Oğünç, A., Cetinel, S., Gedik, N., and Yeğen, B.C. (2006). Ginkgo biloba extract protects against ionizing radiation-induced oxidative organ damage in rats. Pharmacol. Res. *53*, 241–252. https://doi.org/10.1016/j.phrs.2005.11.006.

239. Yurekli, A.I., Ozkan, M., Kalkan, T., Saybasili, H., Tuncel, H., Atukeren, P., Gumustas, K., and Seker, S. (2006). GSM base station electromagnetic radiation and oxidative stress in rats. Electromagn. Biol. Med. *25*, 177–188.

240. Mailankot, M., Kunnath, A.P., Jayalekshmi, H., Koduru, B., and Valsalan, R. (2009). Radio frequency electromagnetic radiation (RF-EMR) from GSM (0.9/1.8GHz) mobile phones induces oxidative stress and reduces sperm motility in rats. Clinics *64*, 561–565.

241. Moussa, S. (2009). Oxidative stress in rats exposed to microwave radiation. Romanian J Biophys *19*, 149–158.

242. Saada, H.N., Rezk, R.G., and Eltahawy, N.A. (2010). Lycopene protects the structure of the small intestine against gamma-radiation-induced oxidative stress. Phytother Res. *24* (*Suppl 2*), S204–S208. https://doi.org/10.1002/ptr.3091.

243. Esmekaya, M.A., Ozer, C., and Seyhan, N. (2011). 900 MHz pulse-modulated radiofrequency radiation induces oxidative stress on heart, lung, testis and liver tissues. Gen. Physiol. Biophys. *30*, 84–89. https://doi.org/10.4149/gpb_2011_01_84.

244. Azzam, E.I., Jay-Gerin, J.P., and Pain, D. (2012). Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury. Cancer Lett. *327*, 48–60. https://doi.org/10.1016/j.canlet.2011.12.012.

245. Bruskov, V.I., Karp, O.E., Garmash, S.A., Shtarkman, I.N., Chernikov, A.V., and Gudkov, S.V. (2012). Prolongation of oxidative stress by long-lived reactive protein species induced by X-ray radiation and their genotoxic action. Free Radic. Res. *46*, 1280–1290. https://doi.org/10.3109/10715762.2012.709316.

246. Ceyhan, A.M., Akkaya, V.B., Güleçol, Ş.C., Ceyhan, B.M., Özgüner, F., and Chen, W. (2012). Protective effects of beta-glucan against oxidative injury induced by 2.45-GHz electromagnetic radiation in the skin tissue of rats. Arch. Dermatol. Res. *304*, 521–527. https://doi.org/10.1007/s00403-012-1205-9.

247. Cosar, R., Eskiocak, S., Yurut Caloglu, V., Ozen, A., Uzal, C., Caloglu, M., Ibis, K., Turan, N., Denizil, B., Saynak, M., et al. (2012). Can radiation-induced chronic oxidative stress in kidney and liver be prevented by dimethylsulfoxide? Biochemical determination by serum and tissue markers. J buon *17*, 160–167.

248. Datta, K., Suman, S., Kallakury, B.V.S., and Fornace, A.J., Jr. (2012). Exposure to heavy ion radiation induces persistent oxidative stress in mouse intestine. PLoS One *7*, e42224. https://doi.org/10.1371/journal.pone.0042224 PONE-D-12-10169.

249. Demirel, S., Doganay, S., Turkoz, Y., Dogan, Z., Turan, B., and Firat, P.G.B. (2012). Effects of third generation mobile phone-emitted electromagnetic radiation on oxidative stress parameters in eye tissue and blood of rats. Cutan. Ocul. Toxicol. *31*, 89–94. https://doi.org/10.3109/15569527.2012.657725.

250. Freitinger Skalická, Z., Zölzer, F., Beránek, L., and Racek, J. (2012). Indicators of oxidative stress after ionizing and/or non-ionizing radiation: superoxid dismutase and malondialdehyde. J. Photochem. Photobiol., B *117*, 111–114. https://doi.org/10.1016/j.jphotobiol.2012.08.009.

251. Kimura, M., Rabbani, Z.N., Zodda, A.R., Yan, H., Jackson, I.L., Polascik, T.J., Donatucci, C.F., Moul, J.W., Vujaskovic, Z., and Koontz, B.F. (2012). Role of oxidative stress in a rat model of radiation-induced erectile dysfunction. J. Sex. Med. *9*, 1535–1549. https://doi.org/10.1111/j.1743-6109.2012.02716.x.

252. Megha, K., Deshmukh, P.S., Banerjee, B.D., Tripathi, A.K., and Abegaonkar, M.P. (2012). Microwave radiation induced oxidative stress, cognitive impairment and inflammation in brain of Fischer rats. Indian J. Exp. Biol. *50*, 889–896.

253. Zhang, Y., Zhang, X., Rabbani, Z.N., Jackson, I.L., and Vujaskovic, Z. (2012). Oxidative stress mediates radiation lung injury by inducing apoptosis. Int. J. Radiat. Oncol. Biol. Phys. *83*, 740–748. https://doi.org/10.1016/j.ijrobp.2011.08.005.

254. Bilgici, B., Akar, A., Avci, B., and Tuncel, O.K. (2013). Effect of 900 MHz radiofrequency radiation on oxidative stress in rat brain and serum. Electromagn. Biol. Med. *32*, 20–29. https://doi.org/10.3109/15368378.2012.699012.

255. Deshmukh, P.S., Banerjee, B.D., Abegaonkar, M.P., Megha, K., Ahmed, R.S., Tripathi, A.K., and Mediratta, P.K. (2013). Effect of low level microwave radiation exposure on cognitive function and oxidative stress in rats. Indian J. Biochem. Biophys. *50*, 114–119.

256. Gultekin, F.A., Bakkal, B.H., Guven, B., Tasdoven, I., Bektas, S., Can, M., and Comert, M. (2013). Effects of ozone oxidative preconditioning on radiation-induced organ damage in rats. J. Radiat. Res. *54*, 36–44. https://doi.org/10.1093/jrr/rrs073.

257. Antunes-Madeira, M.C., and Madeira, V.M. (1979). Interaction of insecticides with lipid membranes. Biochim. Biophys. Acta *550*, 384–392.

258. Moya-Quiles, M.R., Muñoz-Delgado, E., and Vidal, C.J. (1995). Effect of the pyrethroid insecticide allethrin on membrane fluidity. Biochem. Mol. Biol. Int. *36*, 1299–1308.

259. Venkatesan, R., Park, Y.U., Ji, E., Yeo, E.J., and Kim, S.Y. (2017). Malathion increases apoptotic cell death by inducing lysosomal membrane permeabilization in N2a neuroblastoma cells: a model for neurodegeneration in Alzheimer's disease. Cell Death Discov. *3*, 17007. https://doi.org/10.1038/cddiscovery.2017.7.

260. Tiemann, U., Pöhland, R., Küchenmeister, U., and Viergutz, T. (1998). Influence of organochlorine pesticides on transmembrane potential, oxidative activity, and ATP-induced calcium release in cultured bovine oviductal cells. Reprod. Toxicol. *12*, 551–557.

261. Grosicka-Maciąg, E. (2011). [Biological consequences of oxidative stress induced by pesticides]. Postepy Hig. Med. Dosw. *65*, 357–366.

262. Błasiak, J., and Walter, Z. (1992). Protective action of cholesterol against changes in membrane fluidity induced by malathion. Acta Biochim. Pol. *39*, 49–52.

263. Joly Condette, C., Khorsi-Cauet, H., Morlière, P., Zabijak, L., Reygner, J., Bach, V., and Gay-Quéheillard, J. (2014). Increased gut permeability and bacterial translocation after chronic chlorpyrifos exposure in rats. PLoS One *9*, e102217. https://doi.org/10.1371/journal.pone.0102217 PONE-D-14-01044.

264. Krivoshiev, B.V., Dardenne, F., Blust, R., Covaci, A., and Husson, S.J. (2015). Elucidating toxicological mechanisms of current flame retardants using a bacterial gene profiling assay. Toxicol. Vitro *29*, 2124–2132. https://doi.org/10.1016/j.tiv.2015.09.001.

265. Gao, J., Naughton, S.X., Wulff, H., Singh, V., Beck, W.D., Magrane, J., Thomas, B., Kaidery, N.A., Hernandez, C.M., and Terry, A.V., Jr. (2016). Diisopropylfluorophosphate impairs the transport of membrane-Bound Organelles in rat cortical Axons. J. Pharmacol. Exp. Ther. *356*, 645–655. https://doi.org/10.1124/jpet.115.230839.

266. Kvam, E., and Dahle, J. (2005). The pheomelanin precursor 5-S-cysteinyldopa protects melanocytes from membrane damage induced by ultraviolet A radiation. Cancer Lett. *221*, 131–134. https://doi.org/10.1016/j.canlet.2004.08.025.

267. Mishra, K.P. (2004). Cell membrane oxidative damage induced by gamma-radiation and apoptotic sensitivity. J. Environ. Pathol. Toxicol. Oncol. *23*, 61–66.

268. Dihel, L.E., Smith-Sonneborn, J., and Middaugh, C.R. (1985). Effects of an extremely low frequency electromagnetic field on the cell division rate and plasma membrane of Paramecium tetraurelia. Bioelectromagnetics *6*, 61–71.

269. Bhosle, S.M., Pandey, B.N., Huilgol, N.G., and Mishra, K.P. (2002). Membrane oxidative damage and apoptosis in cervical carcinoma cells of patients after radiation therapy. Methods Cell Sci. *24*, 65–68.

270. Bauréus Koch, C.L.M., Sommarin, M., Persson, B.R.R., Salford, L.G., and Eberhardt, J.L. (2003). Interaction between weak low frequency magnetic fields and cell membranes. Bioelectromagnetics *24*, 395–402. https://doi.org/10.1002/bem.10136.

271. Wang, C., Cong, J., Xian, H., Cao, X., Sun, C., and Wu, K. (2002). [The effects of electromagnetic pulse on fluidity and lipid peroxidation of mitochondrial membrane]. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi *20*, 266–268.

272. Capri, M., Mesirca, P., Remondini, D., Carosella, S., Pasi, S., Castellani, G., Franceschi, C., Bersani, F., Schiavoni, A., Castellani, G., et al. (2004). xIn vitro exposure of human lymphocytes to 900 MHz CW and GSM modulated radiofrequency: studies of proliferation, apoptosis and mitochondrial membrane potential X - NO EFFECT. Phys. Biol. *1*, 211–219.

273. Xi, G., Yang, Y.J., and Lu, H. (2009). [Fluorescence used to investigate the sensitivity of spinach chloroplast membrane to low intensity electromagnetic radiation]. Guang Pu Xue Yu Guang Pu Fen Xi *29*, 1920–1924.

274. Ketabi, N., Mobasheri, H., and Faraji-Dana, R. (2015). Electromagnetic fields (UHF) increase voltage sensitivity of membrane ion channels; possible indication of cell phone effect on living cells. Electromagn. Biol. Med. *34*, 1–13. https://doi.org/10.3109/15368378.2013.844706.

275. Zhang, X.F., Ding, C.L., Liu, H., Liu, L.H., and Zhao, C.Q. (2011). Protective effects of ion-imprinted chitooligosaccharides as uranium-specific chelating agents against the cytotoxicity of depleted uranium in human kidney cells. Toxicology *286*, 75–84. https://doi.org/10.1016/j.tox.2011.05.011.

276. Møller, P., Jacobsen, N.R., Folkmann, J.K., Danielsen, P.H., Mikkelsen, L., Hemmingsen, J.G., Vesterdal, L.K., Forchhammer, L., Wallin, H., and Loft, S. (2010). Role of oxidative damage in toxicity of particulates. Free Radic. Res. *44*, 1–46. https://doi.org/10.3109/10715760903300691.

277. Knight-Lozano, C.A., Young, C.G., Burow, D.L., Hu, Z.Y., Uyeminami, D., Pinkerton, K.E., Ischiropoulos, H., and Ballinger, S.W. (2002). Cigarette smoke exposure and hypercholesterolemia increase mitochondrial damage in cardiovascular tissues. Circulation *105*, 849–854.

278. Golomb, E., Matza, D., Cummings, C.A., Schwalb, H., Kodavanti, U.P., Schneider, A., Houminer, E., Korach, A., Nyska, A., and Shapira, O.M. (2012). Myocardial mitochondrial injury induced by pulmonary exposure to particulate matter in rats. Toxicol. Pathol. *40*, 779–788. https://doi.org/10.1177/0192623312441409.

279. Yang, Y.M., and Liu, G.T. (2003). Injury of mouse brain mitochondria induced by cigarette smoke extract and effect of vitamin C on it in vitro. Biomed. Environ. Sci. *16*, 256–266.

280. Lee, H.C., Lu, C.Y., Fahn, H.J., and Wei, Y.H. (1998). Aging- and smoking-associated alteration in the relative content of mitochondrial DNA in human lung. FEBS Lett. *441*, 292–296.

281. Vayssier-Taussat, M., Kreps, S.E., Adrie, C., Dall'Ava, J., Christiani, D., and Polla, B.S. (2002). Mitochondrial membrane potential: a novel biomarker of oxidative environmental stress. Environ. Health Perspect. *110*, 301–305.

282. Saleh, A.M., Vijayasarathy, C., Masoud, L., Kumar, L., Shahin, A., and Kambal, A. (2003). Paraoxon induces apoptosis in EL4 cells via activation of mitochondrial pathways. Toxicol. Appl. Pharmacol. *190*, 47–57.

283. Clarke, R., Connolly, L., Frizzell, C., and Elliott, C.T. (2015). Challenging conventional risk assessment with respect to human exposure to multiple food contaminants in food: a case study using maize. Toxicol. Lett. *238*, 54–64. https://doi.org/10.1016/j.toxlet.2015.07.006.

284. Sharma, H., Zhang, P., Barber, D.S., and Liu, B. (2010). Organochlorine pesticides dieldrin and lindane induce cooperative toxicity in dopaminergic neurons: role of oxidative stress. Neurotoxicology *31*, 215–222. https://doi.org/10.1016/j.neuro.2009.12.007.

285. Moreno, A.J.M., Serafim, T.L., Oliveira, P.J., and Madeira, V.M.C. (2007). Inhibition of mitochondrial bioenergetics by carbaryl is only evident for higher concentrations – Relevance for carbaryl toxicity mechanisms. Chemosphere *66*, 404–411.

286. Kannan, S. (2006). Free radical theory of autoimmunity. Theor. Biol. Med. Model. *3*. https://doi.org/10.1186/1742-4682-3-22.

287. Mostafa, G.A., El-Hadidi, E.S., Hewedi, D.H., and Abdou, M.M. (2010). Oxidative stress in Egyptian children with autism: relation to autoimmunity. J. Neuroimmunol. *219*, 114–118. https://doi.org/10.1016/j.jneuroim.2009.12.003.

288. Wu, G.S., Zhang, J., and Rao, N.A. (1997). Peroxynitrite and oxidative damage in experimental autoimmune uveitis. Invest. Ophthalmol. Vis. Sci. *38*, 1333–1339.

289. Iuchi, Y., Kibe, N., Tsunoda, S., Suzuki, S., Mikami, T., Okada, F., Uchida, K., and Fujii, J. (2010). Implication of oxidative stress as a cause of autoimmune hemolytic anemia in NZB mice. Free Radic. Biol. Med. *48*, 935–944. https://doi.org/10.1016/j.freeradbiomed.2010.01.012.

290. Maes, M., Kubera, M., Mihaylova, I., Geffard, M., Galecki, P., Leunis, J.C., and Berk, M. (2013). Increased autoimmune responses against auto-epitopes modified by oxidative and nitrosative damage in depression: implications for the pathways to chronic depression and neuroprogression. J. Affect. Disord. *149*, 23–29. https://doi.org/10.1016/j.jad.2012.06.039.

291. Shah, A.A., and Sinha, A.A. (2013). Oxidative stress and autoimmune skin disease. Eur. J. Dermatol. *23*, 5–13. https://doi.org/10.1684/ejd.2012.1884.

292. Baser, H., Can, U., Baser, S., Yerlikaya, F.H., Aslan, U., and Hidayetoglu, B.T. (2015). Assesment of oxidative status and its association with thyroid autoantibodies in patients with euthyroid autoimmune thyroiditis. Endocrine *48*, 916–923. https://doi.org/10.1007/s12020-014-0399-3.

293. Malaguti, C., La Guardia, P.G., Leite, A.C.R., Oliveira, D.N., de Lima Zollner, R.L., Catharino, R.R., Vercesi, A.E., and Oliveira, H.C.F. (2014). Oxidative stress and susceptibility to mitochondrial permeability transition precedes the onset of diabetes in autoimmune non-obese diabetic mice. Free Radic. Res. *48*, 1494–1504. https://doi.org/10.3109/10715762.2014.966706.

294. Khan, M.W.A., Banga, K., Mashal, S.N., and Khan, W.A. (2011). Detection of autoantibodies against reactive oxygen species modified glutamic acid decarboxylase-65 in type 1 diabetes associated complications. BMC Immunol. *12*, 1471–2172. https://doi.org/10.1186/1471-2172-12-19.

295. Ahsan, H., Ali, A., and Ali, R. (2003). Oxygen free radicals and systemic autoimmunity. Clin. Exp. Immunol. *131*, 398–404.

296. Liu, Y., Zhu, B., Wang, X., Luo, L., Li, P., Paty, D.W., and Cynader, M.S. (2003). Bilirubin as a potent antioxidant suppresses experimental autoimmune encephalomyelitis: implications for the role of oxidative stress in the development of multiple sclerosis. J. Neuroimmunol. *139*, 27–35.

297. Khurana, R.N., Parikh, J.G., Saraswathy, S., Wu, G.S., and Rao, N.A. (2008). Mitochondrial oxidative DNA damage in experimental autoimmune uveitis. Invest. Ophthalmol. Vis. Sci. *49*, 3299–3304. https://doi.org/10.1167/iovs.07-1607.

298. Kalousová, M., Fialová, L., Skrha, J., Zima, T., Soukupová, J., Malbohan, I.M., and Stípek, S. (2004). Oxidative stress, inflammation and autoimmune reaction in type 1 and type 2 diabetes mellitus. Prague Med. Rep. *105*, 21–28.

299. Mostafalou, S., and Abdollahi, M. (2013). Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. Toxicol. Appl. Pharmacol. *268*, 157–177. https://doi.org/10.1016/j.taap.2013.01.025.

300. Rosenberg, A.M., Semchuk, K.M., McDuffie, H.H., Ledingham, D.L., Cordeiro, D.M., Cessna, A.J., Irvine, D.G., Senthilselvan, A., and Dosman, J.A. (1999). Prevalence of antinuclear antibodies in a rural population. J. Toxicol. Environ. Health *57*, 225–236.

301. D.D Memorandum (1997). Contaminated immune globulin (gammaglobulin) and the Gulf War. CMAT Control # 20002242-0000003 4-15-97.To xxgw.la.osd.mil (name blanked out).

302. DoD Memorandum (1990). Subject: Purchase of Immune Serum Globulin (ISG) from Foreign Manufacturer – ACTION MEMORANDUM. From Frederick J. Erdtmann, Colonel, NC, Chief, Preventive and Military Medicine Consultants Division; to Ronald R. Blanck, Brigadier General, MC, Director, Professional Services. Memorandum through Deputy Director, Professional Services for Director, Professional Services. Department of the Army, Office of the Surgeon General. Nov *29*, 1990.

303. Gabriel, C.M., Gregson, N.A., Redford, E.J., Davies, M., Smith, K.J., and Hughes, R.A. (1997). Human immunoglobulin ameliorates rat experimental autoimmune neuritis. Brain *120* (Pt 9), 1533–1540.

304. Ritch, P.S., and Anderson, T. (1987). Reversal of autoimmune hemolytic anemia associated with chronic lymphocytic leukemia following high-dose immunoglobulin. Cancer *60*, 2637–2640.

305. Joo, S.-J., and Betts, N.M. (1996). Copper intakes and consumption patterns of chocolate foods as sources of copper for individuals in the 1987–1988 Nationwide Food Consumption Survey. Nutr. Res. *16*, 41–52.

306. Wang, B., Feng, L., Jiang, W.D., Wu, P., Kuang, S.Y., Jiang, J., Tang, L., Tang, W.N., Zhang, Y.A., Liu, Y., and Zhou, X.Q. (2015). Copper-induced tight junction mRNA expression changes, apoptosis and antioxidant responses via NF-kappaB, TOR and Nrf2 signaling molecules in the gills of fish: preventive role of arginine. Aquat. Toxicol. *158*, 125–137. https://doi.org/10.1016/j.aquatox.2014.10.025.

307. Miller, R. (2022). NutriGenomic provider seminar. In Functional Genomic Webinar Apr 14, p. 2022.

308. Avery, S.V., Howlett, N.G., and Radice, S. (1996). Copper toxicity towards

Saccharomyces cerevisiae: dependence on plasma membrane fatty acid composition. Appl. Environ. Microbiol. *62*, 3960–3966.

309. Naviaux, R.K., Naviaux, J.C., Li, K., Wang, L., Monk, J.M., Bright, A.T., Koslik, H.J., Ritchie, J.B., and Golomb, B.A. (2019). Metabolic features of gulf war illness. PLoS One *14*, e0219531. https://doi.org/10.1371/journal.pone.0219531 PONE-D-18-35317.

310. Mehta, R., Templeton, D.M., and O'brien, P.J. (2006). Mitochondrial involvement in genetically determined transition metal toxicity II. Copper toxicity. Chem. Biol. Interact. *163*, 77–85. https://doi.org/10.1016/j.cbi.2006.05.011.

311. Haley, R.W., and Kurt, T.L. (1997). Self-reported exposure to neurotoxic chemical combinations in the Gulf War. A cross-sectional epidemiologic study. J. Am. Med. Assoc. *277*, 231–237.

312. Haley, R.W. (2003). Excess incidence of ALS in young Gulf War veterans. Neurology *61*, 750–756.

313. Horner, R.D., Kamins, K.G., Feussner, J.R., Grambow, S.C., Hoff-Lindquist, J., Harati, Y., Mitsumoto, H., Pascuzzi, R., Spencer, P.S., Tim, R., et al. (2003). Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. Neurology *61*, 742–749.

314. Coffman, C.J., Horner, R.D., Grambow, S.C., and Lindquist, J.; VA Cooperative Studies Program Project #500 (2005). Estimating the occurrence of amyotrophic lateral sclerosis among Gulf War (1990-1991) veterans using capture-recapture methods. Neuroepidemiology *24*, 141–150.

315. Avery, S.V., Smith, S.L., Ghazi, A.M., and Hoptroff, M.J. (1999). Stimulation of strontium accumulation in linoleate-enriched Saccharomyces cerevisiae is a result of reduced Sr2+ efflux. Appl. Environ. Microbiol. *65*, 1191–1197.

316. Rossi, L., Marchese, E., Lombardo, M.F., Rotilio, G., and Ciriolo, M.R. (2001). Increased susceptibility of copper-deficient neuroblastoma cells to oxidative stress-mediated apoptosis. Free Radic. Biol. Med. *30*, 1177–1187.

317. Craddock, T.J.A., Harvey, J.M., Nathanson, L., Barnes, Z.M., Klimas, N.G., Fletcher, M.A., and Broderick, G. (2015). Using gene expression signatures to identify novel treatment strategies in gulf war illness. BMC Med. Genomics *8*, 36. https://doi.org/10.1186/s12920-015-0111-3.

318. Broderick, G., Ben-Hamo, R., Vashishtha, S., Efroni, S., Nathanson, L., Barnes, Z., Fletcher, M.A., and Klimas, N. (2013). Altered immune pathway activity under exercise challenge in Gulf War Illness: an exploratory analysis. Brain Behav. Immun. *28*, 159–169. https://doi.org/10.1016/j.bbi.2012.11.007.

319. Whistler, T., Fletcher, M.A., Lonergan, W., Zeng, X.R., Lin, J.M., Laperriere, A., Vernon, S.D., and Klimas, N.G. (2009). Impaired immune function in gulf war illness. BMC Med. Genomics *2*. https://doi.org/10.1186/1755-8794-2-12.

320. Gyulkhandanyan, A.V., Feeney, C.J., and Pennefather, P.S. (2003). Modulation of mitochondrial membrane potential and reactive oxygen species production by copper in astrocytes. J. Neurochem. *87*, 448–460.

321. Tang, C., Luo, J., Yan, X., Huang, Q., Huang, Z., Luo, Q., Lan, Y., Chen, D., Zhang, B., Chen, M., and Kong, D. (2022). Melanin nanoparticles enhance the neuroprotection of mesenchymal stem cells against hypoxic-ischemic injury by inhibiting apoptosis and upregulating antioxidant defense. Cell Biol. Int. *46*, 933–946. https://doi.org/10.1002/cbin.11781.

322. Oh, J.J., Kim, J.Y., Son, S.H., Jung, W.J., Kim, D.H., Seo, J.W., and Kim, G.H. (2021). Fungal melanin as a biocompatible broad-spectrum sunscreen with high antioxidant activity. RSC Adv. *11*, 19682–19689. https://doi.org/10.1039/d1ra02583j.

323. Krause, R., Bühring, M., Hopfenmüller, W., Holick, M.F., and Sharma, A.M. (1998). Ultraviolet B and blood pressure. Lancet *352*, 709–710. https://doi.org/10.1016/S0140-6736(05)60827-6.

324. Marampon, F., Gravina, G.L., Festuccia, C., Popov, V.M., Colapietro, A., Sanità, P., Musio, D., De Felice, F., Lenzi, A., Jannini, E.A., et al. (2016). Vitamin D protects endothelial cells from irradiation-induced senescence and apoptosis by modulating MAPK/SirT1 axis. J. Endocrinol. Invest. *39*, 411–422. https://doi.org/10.1007/s40618-015-0381-9.

325. Diker-Cohen, T., Koren, R., Liberman, U.A., and Ravid, A. (2003). Vitamin D protects keratinocytes from apoptosis induced by osmotic shock, oxidative stress, and tumor necrosis factor. Ann. N. Y. Acad. Sci. *1010*, 350–353.

326. Fedirko, V., Bostick, R.M., Long, Q., Flanders, W.D., McCullough, M.L., Sidelnikov, E., Daniel, C.R., Rutherford, R.E., and Shaukat, A. (2010). Effects of supplemental vitamin D and calcium on oxidative DNA damage marker in normal colorectal mucosa: a randomized clinical trial. Cancer Epidemiol. Biomarkers Prev. *19*, 280–291. https://doi.org/10.1158/1055-9965.EPI-09-0448.

327. Zhang, H.L., and Wu, J. (2010). Role of vitamin D in immune responses and autoimmune diseases, with emphasis on its role in multiple sclerosis. Neurosci. Bull. *26*, 445–454. https://doi.org/10.1007/s12264-010-0731-8.

328. Bockow, B., and Kaplan, T.B. (2013). Refractory immune thrombocytopenia successfully treated with high-dose vitamin D supplementation and hydroxychloroquine: two case reports. J. Med. Case Rep. *7*. https://doi.org/10.1186/1752-1947-7-91.

329. Erkkola, M., Nwaru, B.I., and Viljakainen, H.T. (2011). Maternal vitamin D during pregnancy and its relation to immune-mediated diseases in the offspring. Vitam. Horm. *86*, 239–260. https://doi.org/10.1016/B978-0-12-386960-9.00010-1.

330. Cantorna, M.T., and Mahon, B.D. (2004). Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence. Exp. Biol. Med. *229*, 1136–1142.

331. Sinha, A., Hollingsworth, K.G., Ball, S., and Cheetham, T. (2013). Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. J. Clin. Endocrinol. Metab. *98*, E509–E513. https://doi.org/10.1210/jc.2012-3592.

332. Bischoff, H.A., Stähelin, H.B., Dick, W., Akos, R., Knecht, M., Salis, C., Nebiker, M., Theiler, R., Pfeifer, M., Begerow, B., et al. (2003). Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. J. Bone Miner. Res. *18*, 343–351.

333. Kirn, T.F. (2001). Vitamin D lowered risk of falling in nursing homes by 49%. Fam. Pract. News *6*, 38643.

334. Gendelman, O., Itzhaki, D., Makarov, S., Bennun, M., and Amital, H. (2015). A randomized double-blind placebo-controlled study adding high dose vitamin D to analgesic regimens in patients with musculoskeletal pain. Lupus *24*, 483–489. https://doi.org/10.1177/0961203314558676.

335. Davoudi, M., Allame, Z., Niya, R.T., Taheri, A.A., and Ahmadi, S.M. (2021). The synergistic effect of vitamin D supplement and mindfulness training on pain severity, pain-related disability and neuropathy-specific quality of life dimensions in painful diabetic neuropathy: a randomized clinical trial with placebo-controlled. J. Diabetes Metab. Disord. *20*, 49–58. https://doi.org/10.1007/s40200-020-00700-3.

336. Yao, T., Ying, X., Zhao, Y., Yuan, A., He, Q., Tong, H., Ding, S., Liu, J., Peng, X., Gao, E., et al. (2015). Vitamin D receptor activation protects against myocardial reperfusion injury through inhibition of apoptosis and modulation of autophagy. Antioxid. Redox Signal. *22*, 633–650. https://doi.org/10.1089/ars.2014.5887.

337. Nakai, K., Fujii, H., Kono, K., Goto, S., Kitazawa, R., Kitazawa, S., Hirata, M., Shinohara, M., Fukagawa, M., and Nishi, S. (2014). Vitamin D activates the Nrf2-Keap1 antioxidant pathway and ameliorates Nephropathy in diabetic rats. Am. J. Hypertens. *27*, 586–595. https://doi.org/10.1093/ajh/hpt160.

338. Moore, M.E., Piazza, A., McCartney, Y., and Lynch, M.A. (2005). Evidence that vitamin D3 reverses age-related inflammatory changes in the rat hippocampus. Biochem. Soc. Trans. *33*, 573–577.

339. Koch, C.J., Stobbe, C.C., and Baer, K.A. (1986). Combined radiation-protective and radiation-sensitizing agents. III: Radiosensitization by misonidazole as a function of concentrations of endogenous glutathione or exogenous thiols. Int. J. Radiat. Oncol. Biol. Phys. *12*, 1151–1155.

340. Cholon, A., Giaccia, A.J., Lewis, A.D., Hickson, I., and Brown, J.M. (1992). What role do glutathione S-transferases play in the cellular response to ionizing radiation? Int. J. Radiat. Oncol. Biol. Phys. *22*, 759–763.

341. Yun, M.J., Kang, D.M., Lee, K.H., Kim, Y.K., and Kim, J.E. (2013). Multiple chemical sensitivity caused by exposure to ignition coal fumes: a case report. Ann. Occup. Environ. Med. *25*, 32. https://doi.org/10.1186/2052-4374-25-32.

342. Fukuda, K., Nisenbaum, R., Stewart, G., Thompson, W.W., Robin, L., Washko, R.M., Noah, D.L., Barrett, D.H., Randall, B., Herwaldt, B.L., et al. (1998). Chronic multisymptom illness affecting Air Force veterans of the gulf war. Journal of the American Medical Association *280*, 981–988.

343. Institute of Medicine (2002). The Anthrax Vaccine. Is it Safe? Does it Work? (National Academy Press).

344. Garcia-Irigoyen, O., Bovenga, F., Piglionica, M., Piccinin, E., Cariello, M., Arconzo, M., Peres, C., Corsetto, P.A., Rizzo, A.M., Ballanti, M., et al. (2022). Enterocyte superoxide dismutase 2 deletion drives obesity. iScience *25*, 103707. https://doi.org/10.1016/j.isci.2021.103707.

345. Faul, F., Erdfelder, E., Buchner, A., and Lang, A.G. (2009). Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behav. Res. Methods *41*, 1149–1160. https://doi.org/10.3758/BRM.41.4.1149.

346. Faul, F., Erdfelder, E., Lang, A.G., and Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods *39*, 175–191.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
Stata Versions 9.0 and 12.0	College Station, Texas	https://www.stata.com
G*Power Version 3.1.9.7	Faul et al.[345,346]	https://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Beatrice A. Golomb, MD, PhD (bgolomb@ucsd.edu).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- All data reported in this paper will be shared by the lead contact upon request.
- This paper does not report original code.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Human participants

Table 1 shows the breakdown of age, gender, and ethnicity. The majority of participants were male and Caucasian, consistent with the demographic composition of those deployed to the Persian Gulf. Socioeconomic status was not separately assessed. 81 participants included 41 veterans with Gulf War illness and 40 controls matched 1:1 to 40 of the cases on sex, age, and ethnicity (designated by the participant). An additional case completed the study; recruitment had continued until there were 40 matched pairs, and for this individual case, a matched control had not at that time been identified. Since analyses here are cross-sectional (the primary purpose is not to compare cases to controls, but to look at relationships across and within these groups), the additional case provides additional relevant information on the relation of exposures to outcomes, and is included. Biological sex best describes the data. The dearth of female participants (consistent with the small fraction of Gulf deployed personnel that were female) precludes meaningful sex-stratified analysis. The parent study from which the data were secured was approved by the UC San Diego Human Research Protections Program (**HRPP**) and the Department of Defense (**DoD**) Human Research Protection Office (**HRPO**). All participants gave written informed consent.

METHOD DETAILS

This study encompasses case-control and cross-sectional design elements. We assess propensity to experience adverse events to exposures (AE Propensity) in VGWI vs. matched healthy controls. We assess the cross-sectional relationships between individual exposures and AE Propensity, in the total sample and in GWI cases and healthy controls separately. Participants were obviously not randomized to exposures in the Gulf. As this is not a treatment study, randomization did not occur. All participants and study staff were blinded to the intent to assess adverse effect propensity, or to relate it to Gulf exposures.

To qualify as a GWI case, veterans must have been deployed to the Persian Gulf theater of operations between August 1, 1990 and July 31, 1991, inclusive. VGWI were additionally required to meet both CDC and Kansas symptom inclusion criteria for GWI.[3,342] CDC criteria require presence of symptoms for at least

6 months, arising during or after Gulf War participation, in at least two of the three domains of fatigue/sleep, mood-cognitive, and musculoskeletal.[342] The more discriminating, more specific Kansas criteria require that symptoms have been present for at least 6 months, arising during or after Gulf deployment, in at least three of a suite of six categories comprising fatigue/sleep, pain, neurological/cognitive/mood, respiratory, gastrointestinal, and dermatologic.[3] For a symptom domain to qualify toward Kansas symptom criteria, the component symptoms must be at least moderate in severity (not mild) and/or there must be multiple symptoms within the domain.[3]

To qualify as a control, it was required that participants were nonveterans, meeting neither Kansas nor CDC symptom inclusion criteria for GWI, and additionally not meeting Kansas exclusion criteria (that is, they could not have other health conditions such as lupus or multiple sclerosis that could produce symptoms that could be confused for those of GWI). Controls were selected to match 1:1 to enrolled cases on sex, ethnicity, and age. A half-match for ethnicity was deemed to be qualifying, in recognition of the prevalence of mixed ethnicities. Age matching for matched pairs was within 4 years.

Nonveteran and veteran controls each have advantages and disadvantages. We preferred nonveteran controls. 1. Veterans of the 1990-1 Gulf War who remain healthy despite exposures may have specific protective genetics and/or engage distinct protective adaptations that may render them unsuitable as controls. Gulf era veterans who were not deployed are known to differ significantly: unhealthier persons are not selected for deployment to high threat areas and it has been affirmed that nondeployed era veterans were materially less healthy.[343] Veterans from other conflicts may have experienced other problematic exposures (e.g. antimalarials like mefloquine that may compromise suitability). All military personnel experienced some exposures (e.g. mandatory vaccinations, depleted uranium, permethrin, impregnated uniforms) that may contribute toward shared mechanisms with GWI, reducing statistical power to observe differences. For these reasons, our preference is for nonveteran healthy controls. Controls were drawn from rosters of healthy controls used in prior GWI studies, supplemented by outreach primarily through ResearchMatch.

QUANTIFICATION AND STATISTICAL ANALYSIS

Measurements

Demographic characteristics including age, sex, ethnicity, and marital status were assessed. Military information was collected for VGWI.

GWI-relevant symptoms were gauged by Kansas criteria symptom scores for each Kansas symptom domain.

Exposures were elicited via inquiries for a list of general exposures (non-Gulf specific – see Table 1a); and for veterans, a list of Gulf-specific exposures (see Table 1b). Whether the exposure had been experienced was rated no, unsure, or yes – which were coded as 0, 0.5, and 1, respectively. A summed exposure score (**totExp**) summed responses on queried exposures.

Adverse effects: Those who rated an exposure as "yes" were asked if they had experienced an AE or health effect to the exposure. Response options were again no, unsure, or yes, coded as 0, 0.5, and 1, respectively. A summed adverse effect score (**totAE**) summed responses on the AE queries.

AE Propensity: To gauge a proxy for AE Propensity, a ratio was calculated, of totAE divided by totExp – roughly, the fraction of assessed exposures to which AEs were reported to have been experienced.

Chemical sensitivity: The study assessed self-rated chemical sensitivity via the chemical sensitivity question from the widely-employed Kansas GWI questionnaire, as well as via our single-item UCSD GWI chemical sensitivity self-rating, analyzed as a binary assessment (0 if absent, 1 if present). The Kansas criteria question states: "Having physical or mental symptoms after breathing in certain smells or chemicals." The timeframe for the Kansas query is the prior 6 months, with a 4-point Likart scale as absent, mild, moderate, severe rated 0, 1, 2, 3, respectively. The UCSD self-rating states: "Chemical sensitivity (e.g., unusual sensitivity to smells)." The timeframe is 2 weeks. This was assessed as a binary rating, 0 if absent, 1 if present. The Kansas and UCSD measures show convergent validation against one another: r=0.57, p=0.0001. The single-item UCSD chemical sensitivity measure was further validated by affirming a relation to SOD2 a16v, an

adverse polymorphism of the major mitochondrial antioxidant SOD2,[344] that had elsewhere related to chemical sensitivity in a Japanese cohort.[49]

Missing data in exposure (and AE) tallies, a missing value was treated as absence of the corresponding exposure (or AE).

Analysis

Descriptive statistics characterized participant characteristics, Kansas symptom ratings, totAE, totExp, AE Propensity and the chemical sensitivity measures for all participants, and for cases and controls separately. T-tests and chi-squared tests compared characteristics of cases to those of controls for continuous and categorical variables respectively. Ethnicity was used for matching of controls to cases for case-control assessments, but was otherwise not a focus of the present study.

Summed AEs, summed exposures, and AE Propensity were compared in (all) cases vs. controls (unpaired t-test), The correlations of AE Propensity to Kansas symptom domains and to chemical sensitivity indices were assessed.

We evaluated how individual exposures correlated to AE Propensity, in the total sample, and in cases and controls separately. Correlation in each group was complemented by regression in the total sample, adjusted for case status. All regression analyses used robust standard errors (aka heteroskedasticity-independent standard errors).[60]

Shared relationships among exposures within an exposure class were used to guide generation of composite variables for inclusion in multivariable models (to limit the number of predictors included).

A shared set of predictors were identified for use in multivariable models, spanning all participants (adjusted for case status), and cases and controls separately. These models could not include Gulf-specific exposures, as these were not elicited for controls.

Additional models were individually optimized for all participants, adjusted for case status; for cases; and for controls. For the model specific to cases, Gulf-specific exposures could be included.

After identification of a robust "main" model, a number of variables were assessed for candidacy as added variables (particularly those with $p \lesssim 0.15$ on univariable assessment), and the best identified candidates are shown.

Main models for the combined case-control samples were reassessed in age-stratified analysis (stratified at the mean sample age) to assess internal replication in independent groups.

Key predictors were then reassessed via logistic regression in GWI cases, as predictors of the binary UCSD chemical sensitivity variable.

Analyses used Stata 9.0 and Stata 12.0 (College Station, Texas). Two-sided $p < 0.05$ designated statistical significance. Adjustment for multiple comparisons was not undertaken.

Sample size and power

Analyses capitalized on data procured for a different primary purpose though from the outset, the intention was to assess other exposure/outcome relationships, to enhance yield per dollar expended and more importantly, per Gulf War veteran contribution/burden. The sample size of 40 per group (matched pairs) provides power of 99% to identify a 0.5 SD difference with two-sided alpha of 0.05 (G*Power 3.1.9.7).[345,346] Alternatively, the study has 80% power at two-sided alpha of 0.05 to detect an effect size of ≥ 0.32 standard deviations (strong power for a modest effect size). Power for regression analyses varies by group/subset assessed, but significance for key exposure outcome relationships, upheld in stratified analyses, affords post hoc affirmation of adequate study power for these assessments.

Efforts to reduce bias

(1) Key limitations include prospects for recall and reporting bias, with a material span from Gulf exposures to survey completion. However, an "unsure" response helped capture uncertainty in responses. Moreover, there is not strong rationale for considering that specific exposure classes would be disproportionately reported *in alignment with* adverse effect propensity spanning exposure classes.

(2) Primary models were assessed in all participants, in VGWI and controls separately, and in analysis stratified by age to protect against spurious findings. Assessment of calculated AE Propensity against self-rated chemical sensitivity further reinforces validity of the AE Propensity construct assessed.