New insights on 'old' toxicants in occupational toxicology (Review)

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Abstract. In order to deliver the best possible working environment, it is essential to identify professional conditions that could be harmful for worker's health and prevent (or limit) the occurrence of such conditions. The appropriate use of personal protective equipment and the development of appropriate regulations allowed to reduce the prevalence of 'classic' occupational diseases, such as occupational hearing loss or asbestosis, just to name a few. Nowadays, environmental pollution seems to be one of the most relevant concerns for human and animal health, and toxicology is becoming one of the most prominent fields of interest in occupational settings. An increasing number of studies demonstrate that the presence of toxicants in the workplace could be responsible for the development of chronic diseases, even at doses that were considered 'safe'. The present review summarizes some of the most recent advancements in occupational toxicology, focusing on topics that have long been debated in the past and that have recently returned to the fore.

Contents

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1. Introduction

A huge number of studies have been performed on well known toxicants such as asbestos, pesticides and benzene. Even though there is plenty of evidence toward the toxicity of these compounds, recent findings are pointing out some novelties like new pathogenetic mechanisms, or previously unsuspected work-related pathologies (1).

In occupational settings, it is very important to keep an eye on these toxicants because of their great distribution: pesticides are globally used to enhance agricultural production and to control pests; benzene is still used in petrochemical reactions and its exposure involves many human activities (e.g., gas station attendants); asbestos-like fibers [e.g., carbon nanotubes (CNTs)] are raising great concern in the scientific community because of their increasing use in industry despite their potential, and yet partially known, toxicity (2). The present review summarizes some of the most recent and supported findings on these toxicants.

2. Data collection methods

In the present study, a computerized search on PubMed was performed up to November 2016. Search terms were combinations of the following keywords and their abbreviations: 'carbon nanotubes' and 'toxicity' or 'exposure'. 'Pesticides' and 'chronic diseases' or 'Parkinson' or 'cancer' or 'epigenetics'. 'Benzene' and 'low dose exposure' or 'chronic exposure' or 'epigenetics' or 'exposure' or 'assessment'. References in reports were also reviewed. The attention was focused on recent findings on these toxicants, which could be of particular interest towards occupational exposure. For this reason, *in vivo* studies were generally preferred to *in vitro* studies.

3. Asbestos-like fibers

Fiber-induced pulmonary toxicity was widely debated in the 1990s because of the emerging harmful effects of asbestos, which led to the banning of this material from commerce. Later on, it was demonstrated that the high aspect ratio of asbestos fibers was the main pathogenetic factor, and that other fibers could have the same pathogenicity. This is the case in other natural fibers like fluoro-edenite and in silicon carbides (SiC) (1-6).

Recently, some studies have linked CNT exposure with the same pathologies produced by asbestos exposure, such as pleural plaques, fibrosis, and pleural mesothelioma (7,8). In 2014, the International Agency for Research on Cancer published its conclusions on these 'asbestos-like' fiber (1), assessing fluoro-edenite fibrous amphibole as carcinogenic to human (Group 1). Furthermore, occupational exposure associated with the Acheson process (of which SiC fibres are unwanted byproducts) was also classified as carcinogenic to humans (Group 1), while fibrous SiC was included in Group 2b, as possible carcinogen to humans. Finally, multi-walled CNT-7 (MWCNT-7) was classified as possible carcinogen to humans (Group 2b), while single-walled CNTs (SWCNT) and other forms of MWCNT were recorded as not classifiable for their carcinogenicity to humans (Group 3), for lack of sufficient evidence (1).

CNTs toxicity. A recent review examined the detrimental health effects of asbestos-like fibers, including CNTs (2). The authors found a general consensus about the toxicity of these particles, and their potential toxicity towards the serosal cavities like the pleura and the peritoneum in animal models. In particular, a study in 2008 reported a high incidence of mesothelioma after intraperitoneal injection of MWCNT in mice, and, furthermore, MWCNT injection produced the highest mortality compared to fullerene and crocidolite (9). Another experiment aimed to discover if the presence of structural defects in MWCNTs could be a pathogenetic factor. After intraperitoneal injection in mice of structurally imperfect nanotubes (MWCNT+) and nanotubes without structural defects (MWCNT-) and comparison with a similar dose of crocidolite, the authors found that only crocidolite was capable of inducing mesothelioma (10). The hypothesis that a particular group of MWCNT (with structural defects) could have been more toxic than other types was of particular interest in occupational settings, and the authors of the study concluded that the negative results obtained were attributable to the short length of the MWCNT used for the experiment. According to this hypothesis, later studies confirmed that length is a key parameter in fibrous nanoparticle toxicology (11).

Recently, another review examined the toxicity of carbon nanoparticles and CNTs (CNPs/CNTs) on the respiratory system, especially in occupational settings. The authors found that the majority of studies indicate that CNPs/CNTs induce respiratory system pathologies such as hypersensitivity, inflammation, fibrosis, and cancer and that these nanomaterials are released in the air during their manufacturing and handling (12).

Guseva Canu *et al* reviewed the current knowledge on occupational exposure to CNTs and nanofilaments (13). The authors found that the most exposed subjects are: academic and private laboratory workers, which engineer and elaborate new materials, workers employed at facilities which produce nanomaterials for selling them to the industry (primary workers) and workers employed in industries or laboratories which use the previously produced nanomaterials for the development of final products (secondary workers). The authors concluded that exposure to CNTs/CNFs is possible during the whole life-cycle, even if a real assessment of exposure has been done only for the early stages of production, while information on exposure at final stages of production is lacking. Furthermore, since MWCNTs appear to be the most hazardous material because of its toxicity (1), the majority of studies focus on the exposure/toxicity of this kind of nanotubes. Actually, exposure to SWCNTs and, even more, to carbon nanofilaments (CNFs) is quantitatively even more relevant than to MWCNTs and should be further investigated. On the other hand, consumer exposure seems to be limited.

To date, there is no conclusive data about the toxicity of these molecules on humans, and, furthermore, animal models can only partially indicate the potential toxicity of these materials because of the numerous variants of CNTs and CNFs produced in the facilities. For these reasons, the National Institute for Occupational Safety and Health (NIOSH) recommends maximum caution for any occupational exposure to these materials, which levels have to be maintained below recommended exposure limit. At this time, given the available literature, NIOSH advises not to exceed 1 $\mu g/m^3$ of respirable elemental carbon as 8 h time weighted average for CNT and CNF. Furthermore, these regulations are recommended for any type of CNT and CNF, until scientific evidence will definitively shed light on their actual toxicity.

4. Pesticides

Because of their undisputed utility, pesticides are today an essential tool in agriculture, and many efforts have been made by the scientific community to identify the possible biological and pathological consequences of environmental and professional exposure to pesticides. Assessing professional exposure, though, is far from simple. A previous study of our group summarized the latest findings on the relation between pesticide exposure and development of chronic diseases (14). Even though the link between pesticide exposure and the development of neurological diseases (15,16), reproductive disorders (17,18) and cancer (19-21) seems clear and almost obvious in some cases [like Parkinson's disease (PD)], it is still difficult to correlate these pathologies to exposure to a narrow spectrum of pesticides. Many studies, infact, evaluate exposure to pesticide in general. In particular, epidemiological studies suffer of inaccuracy, because pesticides are almost invariably used as mixtures, so that it is difficult for the worker to remember the exact name of the pesticides he used throughout the years, and for the researcher to determine the specific pesticide which could be responsible for any specific alteration. Furthermore, pesticides are usually applied in open fields, and variables like humidity, wind, heat and correct use of personal protective equipment are almost impossible to be precisely evaluated over a long period of working activity. The use of questionnaires and expert interviews has been used as a tool to provide a more precise assessment of previous exposure of individuals, but the results are still controversial (22,23).

Pesticide tasks. Individuals who are involved in pesticide application processes in agricultural and non-agricultural settings or spend their activity nearby the site of application, are potentially exposed to these toxicants: i) mixer/loaders, individuals perform tasks in preparation for an application. For example, prior to application, mixer/loaders would mix a liquid pesticide concentrate with water and load it into the

holding tank; ii) applicators, individuals operate application equipment during the release of a pesticide product onto its target; iii) mixer/loader/applicators, individuals who perform all aspects of the pesticide application process; iv) flaggers, individuals that guide aerial applicators during the release of a pesticide product onto its target.

Furthermore, other categories of workers can be exposed to pesticides like farmers, greenhouse workers, plants manufacturers, workers responsible of re-entry activities in vineyards or other crops.

Pesticide toxicity. Pesticides, in general, have been linked with a really wide range of pathologies. Cancer at various sites of the body is one of the most discussed themes, as well as neurological diseases. Other pathologies such as diabetes mellitus (24-26), reproductive disorders (27,18) and cardiovascular diseases (28,29) have also been linked to pesticide exposure.

The most consistent findings for the correlation between pesticides and chronic diseases development are with cancer and with Parkinson's disease (PD).

PD is a multifactorial, neurodegenerative disease chiefly characterized by tremor, bradykinesia, rigidity and postural instability as clinical symptoms (30). The main pathogenetic event behind this clinical presentation is the death of dopaminergic cells in the substantia nigra pars compacta, and progressive degeneration of its projections to the basal ganglia. There are numerous studies pointing towards the conclusion that pesticides could be a risk factor for the development of PD, even if the majority of studies did not find a specific bond between a single or a group of pesticides and the disease. The link appeared very likely for pesticides in general, even if it is a heterogeneous group of compounds. In this regard, a meta-analysis performed by Hernández *et al* serves perfectly as an example, since the authors could not draw any specific conclusion (15).

Similar results were attained by Freire and Koifman, who reviewed epidemiological studies between 2000 and 2011 about the connection between organophosphate exposure and PD (31). The authors found several studies reporting a positive correlation between pesticide exposure and PD: in particular, 13 case-control studies reported a significant association. Other studies reported an increase in the risk of developing PD for those subjects who have genetic polymorphism like paraoxonase enzyme 1 and nitric oxide synthase, both involved in detoxification of pesticides, as confirmed by other studies (18). Furthermore, a strong association was reported in particular for clorpyrifos (organophosphate), organochlorines, and for maneb and paraquat, especially when combined.

Another meta-analysis (32) examined 12 cohort studies and concluded that occupational exposure to pesticides is a possible risk factor for the development of PD, even if, once again, they were not able to isolate specific compounds causing the disease.

As evidenced before, methods for a proper assessment of exposure are still under discussion. Nevertheless, some interesting pathogenetic mechanisms are emerging regarding the role of pesticides in the development of chronic diseases, and, in particular, of cancer development.

Pesticides, in fact, have been proved to have immunotoxic properties, through the alteration of cytokine profiles (33). The role of immune system is central in cancer development, as demonstrated by recent investigations: the recognition and destruction of tumor cells is indeed a mechanism of protection for the body, but the development of a chronic inflammatory microenvironment could, on the other hand, support tumor progression (34). So, the immune system can, in turn, promote or contrast cancer progression. This characteristic is known as cancer immunoediting and summarily consists of three phases: i) elimination (immunosurveillance), ii) equilibrium (control of tumor growth) and iii) escape (alteration of tumor cells which elude the immune system or induce immunosuppressive mechanisms, which ultimately lead to tumor growth) (35). The role of pesticides in cancer development could likely include one or more of these mechanisms.

A study by Cassidy *et al* was performed regarding the correlation between exposure to pesticides and breast cancer development. Biopsies of breast lesions were examined and the authors found a positive link between heptachlor epoxide exposure and prevalence of cancer (36).

A study by Lee *et al* demonstrated a link between pesticide exposure and the incidence of lung cancer in pesticide applicators, even after adjusting the results for cigarette smoke and other confounding factors (37). Later on, another study from the same group analyzed a very large cohort of agricultural workers (56,813) - called the agricultural health study cohort - to assess the incidence of colorectal cancer. Given the already known issues regarding occupational exposure assessment in agricultural settings, this study tried to surpass those issues by administering an enrolment questionnaire, followed by a more detailed take-home questionnaire. The questionnaires included information regarding previous exposure up to 50 pesticides and working habits like use of personal protective equipment, equipment status and application methods. Questions regarded also lifestyle habits like physical activity and fruit consumption. The results elucidated a significant connection between the use of some pesticides (chlorpyrifos and aldicarb) and colorectal cancer among these workers, even if this result has to be contextualised as an epidemiological observation which was not supported by pathogenetic hypothesis prior to the study. Besides, the study results could be questioned given the large population analysed, the large number of pesticides included in the questionnaires, and the incidence of colorectal cancer among the general population, even if the design of the study tried to minimize the bias (38). Several studies have been performed on the agricultural health study cohort, and their results have been summarised in a review by Weichenthal *et al* (39). The authors concluded that most of the pesticides examined were not strongly correlated with the incidence of cancer, even if, in some cases, an increased relative risk/odds ratio was registered. Despite these results, further studies are needed to assess the role of pesticides in cancer development.

Interesting results have been attained regarding the exposure to organochlorines and hepatocellular cancer (HCC). A study conducted in California showed a positive association between exposed workers and HCC development in agricultural areas. Similar results were attained in another study, which highlighted an increased prevalence of HCC in

areas contaminated by widespread pesticide use, if compared to the median population values (40).

5. Benzene

Benzene toxicity has been assessed for a long time. Even if the use of this molecule has been limited, it remains necessary in many industrial processes, like the production of styrene, cyclohexane, cumene, inks, solvents, pesticides, lubricants. As a consequence, occupational exposure is still possible (41). Alongside this professional routes of exposure, benzene is also an environmental contaminant mainly because of industrial emissions, automobile service stations, car exhaust gas, and, more importantly, cigarette smoking habits.

It has been demonstrated that benzene exposure is linked with the risk of developing hematological diseases like aplastic anemia, myelodysplastic syndrome, acute and chronic lymphocytic leukemia and cancers like multiple myeloma and non-Hodgkin's lymphoma (42,43). Furthermore, benzene toxicity has been linked to the development of diseases at other sites of the human body, like the respiratory system (44), the immune system (45,46), nervous (47) and reproductive systems (48-50,41). Studies indicate that benzene could be a risk factor for the development of breast cancer (51-53), prostate cancer, stomach cancer, colon cancer, pharyngeal cancer and malignant melanoma (54-57).

Several mechanisms of toxicity have been proposed for benzene, like production of chromosomal aberrations, sister chromatid exchange, and micronuclei (58). Recently, some studies have evidenced that some of the harmful effects of benzene could be caused by the induction of oxidative stress. A recent review (59) simulated chronic exposure to benzene on mice, with the aim to evaluate the mechanism of toxicity of benzene itself and of its metabolite hydroquinone. After the evaluation of plasmatic values for insulin and glucose and the examination of liver and pancreatic histological samples, the authors concluded that repeated administration of benzene could be capable of determining oxidative stress-related damage to the liver and the pancreas (the latter determined by hydroquinone, a benzene metabolite). These results suggest the potential role of benzene in the development of glucose metabolism dysregulations. Even if the study of Bahadar *et al* (59) examined the molecular effects of benzene at relatively high doses, similar pathways may be involved in the pathogenesis of chronic cellular damage at other sites (60), even at low degrees of exposure. In this regard, a study of our group enrolled 91 male gas station attendants and compared them to a control population of 63 male office workers (61). The aim was to evaluate the effects of low dose, chronic exposure to benzene on NF-κB, STAT3, p38-MAPK and stress-activated protein kinase/Jun aminoterminal kinase signal transduction pathways in peripheral blood mononuclear cells of gas station workers. Urine samples were collected at the end of the work shift to evaluate the concentration of trans, trans-muconic acid (t,t-MA), and oxidative stress biomarkers were determined on blood samples. The results showed a significant increase of t,t-MA in the urine of gasoline station attendants, compared with those of the control group. NF-κB and phospho-IκB-α proteins were also higher in the exposed population, while phosphorylated STAT3 was significantly decreased in the benzene exposed group, compared to controls. These results indicate the action of benzene on some oxidative stress-related signal transduction pathways, even at low doses of occupational exposure (61,62).

A similar study conducted by Xia *et al* involved 144 workers, of which 96 were gasoline filling station attendants (with no history of exposure to heavy metals and organic solvents) and 48 were cashiers, the latter used as controls. Aim of the study was to assess the oxidative stress status of workers exposed to benzene, toluene, ethylbenzene, xylene (BTEX) and manganese (Mn) (63). Mn levels were investigated since methylcyclopentadienyl manganese tricarbonyl (MMT), an organic derivative, is a widely used additive for gasoline. The authors combined environmental monitoring with biological monitoring for the assessment of exposure. After that, the authors calculated the cumulative exposure index from 8 h of BTEX and Mn exposure time-weighted average and multiplied this value for the years of exposure. The authors assessed oxidative stress biomarker levels, such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GSH-Px), malondialdehyde (MDA) and Hsp70. Given that the airborne concentration of BTEX were significantly higher in gas station attendants working environment than for office workers, blood levels of SOD and GSH-Px were significantly lower in the exposed group than in the control group, and, conversely, MDA levels (a marker of oxidative stress) were significantly higher in the exposed group, especially for those who had been working in gas stations for a longer time (>10 years). Hsp70 hematic concentration was also found higher in gas station attendants who worked for >10 years in the field, compared to the control group. The authors concluded that MMT-containing gasoline may diminish the antioxidant capabilities of the body and enhance lipid peroxidation levels in occupationally exposed workers. Hsp70 could be an interesting biomarker in this regard.

6. Conclusions and future perspectives

The pollution of living environment and workplaces by a large number of toxic agents, makes it essential to continue investigating the links between exposure to toxicant and development of certain pathologies, basing on epidemiological evidence and laboratory experiments.

Occupational and environmental exposure to CNTs and to nanoparticles in general is particularly important in this regard, as this scenario reminds us of what happened with asbestos some decades ago. Although this comparison may sound exaggerated, the studies presented above show that, even if some international agencies are recommending limits for occupational exposure, occupational and environmental exposure still continues even if the possible consequences are not yet fully clear.

Pesticides exposure shows similar issues. Even after years of investigations, scientific evidence is still conflicting with the fact that a proper assessment of occupational exposure is very difficult to obtain and this corrupts the reliability of a large number of epidemiological and retrospective studies. Recently, the use of algorithms and tools like job exposure matrices has been proposed to surpass this issue and establish the correct links between exposure to specific pesticides and the eventual development of diseases.

Lastly, the examination of some of the latest evidence regarding benzene toxicity points out another very interesting argument. In fact, the evidence that benzene exposure could be related to immunotoxic and epigenetic effects opens new scenarios about individual susceptibility to this molecule (as well as others), and probably leads towards a novel conception of occupational safety. Personal characteristics such as genetic polymorphisms and eventual epigenetic changes should, in fact, be considered for a real assessment of risk in the future.

References

1. Grosse Y, Loomis D, Guyton KZ, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Scoccianti C, Mattock H, *et al*: Carcinogenicity of fluoro-edenite, silicon carbide fibres and whiskers, and carbon nanotubes. Lancet Oncol 15: 1427-1428, 2014.
2. Miozzi E, Rapisarda V, Marconi A, Costa C, Polito I, Spandidos DA, Libra M and Fenga C: Fluoro edenite and carbon nanotubes: The health impact of 'asbestos like' fibres. Exp Ther Med 11: 21-27, 2016.
3. Rapisarda V, Salemi R, Marconi A, Loreto C, Graziano AC, Cardile V, Basile MS, Candido S, Falzone L, Spandidos DA, *et al*: Fluoro-edenite induces fibulin-3 overexpression in non-malignant human mesothelial cells. Oncol Lett 12: 3363-3367, 2016.
4. Ledda C, Loreto C, Matera S, Massimino N, Cannizzaro E, Musumeci A, Migliore M, Fenga C, Pomara C and Rapisarda V: Early effects of fluoro-edenite: Correlation between IL-18 serum levels and pleural and parenchymal abnormalities. Future Oncol 12: 59-62, 2016.
5. Drummond G, Bevan R and Harrison P: A comparison of the results from intra-pleural and intra-peritoneal studies with those from inhalation and intratracheal tests for the assessment of pulmonary responses to inhalable dusts and fibres. Regul Toxicol Pharmacol 81: 89-105, 2016.
6. Boudard D, Forest V, Pourchez J, Boumahdi N, Tomatis M, Fubini B, Guilhot B, Cottier M and Grosseau P: In vitro cellular responses to silicon carbide particles manufactured through the Acheson process: Impact of physico-chemical features on pro-inflammatory and pro-oxidative effects. Toxicol In Vitro 28: 856-865, 2014.
7. Murphy FA, Schinwald A, Poland CA and Donaldson K: The mechanism of pleural inflammation by long carbon nanotubes: Interaction of long fibres with macrophages stimulates them to amplify pro-inflammatory responses in mesothelial cells. Part Fibre Toxicol 9: 8, 2012.
8. Donaldson K, Poland CA, Murphy FA, MacFarlane M, Chernova T and Schinwald A: Pulmonary toxicity of carbon nanotubes and asbestos - similarities and differences. Adv Drug Deliv Rev 65: 2078-2086, 2013.
9. Takagi A, Hirose A, Nishimura T, Fukumori N, Ogata A, Ohashi N, Kitajima S and Kanno J: Induction of mesothelioma in $p53^{+/-}$ mouse by intraperitoneal application of multi-wall carbon nanotube. J Toxicol Sci 33: 105-116, 2008.
10. Muller J, Delos M, Panin N, Rabolli V, Huaux F and Lison D: Absence of carcinogenic response to multiwall carbon nanotubes in a 2-year bioassay in the peritoneal cavity of the rat. Toxicol Sci 110: 442-448, 2009.
11. Schinwald A, Murphy FA, Prina-Mello A, Poland CA, Byrne F, Movia D, Glass JR, Dickerson JC, Schultz DA, Jeffree CE, *et al*: The threshold length for fiber-induced acute pleural inflammation: Shedding light on the early events in asbestos-induced mesothelioma. Toxicol Sci 128: 461-470, 2012.
12. Pacurari M, Lowe K, Tchounwou PB and Kafoury R: A review on the respiratory system toxicity of carbon nanoparticles. Int J Environ Res Public Health 13: E325, 2016.
13. Guseva Canu I, Bateson TF, Bouvard V, Debia M, Dion C, Savolainen K and Yu IJ: Human exposure to carbon-based fibrous nanomaterials: A review. Int J Hyg Environ Health 219: 166-175, 2016.
14. Gangemi S, Miozzi E, Teodoro M, Briguglio G, De Luca A, Alibrando C, Polito I and Libra M: Occupational exposure to pesticides as a possible risk factor for the development of chronic diseases in humans (Review). Mol Med Rep 14: 4475-4488, 2016.
15. Hernández AF, González-Alzaga B, López-Flores I and Lacasaña M: Systematic reviews on neurodevelopmental and neurodegenerative disorders linked to pesticide exposure: Methodological features and impact on risk assessment. Environ Int 92-93: 657-679, 2016.
16. Ritz BR, Paul KC and Bronstein JM: Of pesticides and men: A California story of genes and environment in Parkinson's disease. Curr Environ Health Rep 3: 40-52, 2016.
17. Hanke W and Jurewicz J: The risk of adverse reproductive and developmental disorders due to occupational pesticide exposure: An overview of current epidemiological evidence. Int J Occup Med Environ Health 17: 223-243, 2004.
18. Kumar S: Occupational exposure associated with reproductive dysfunction. J Occup Health 46: 1-19, 2004.
19. Gangemi S, Gofita E, Costa C, Teodoro M, Briguglio G, Nikitovic D, Tzanakakis G, Tsatsakis AM, Wilks MF, Spandidos DA, *et al*: Occupational and environmental exposure to pesticides and cytokine pathways in chronic diseases (Review). Int J Mol Med 38: 1012-1020, 2016.
20. Clapp RW, Jacobs MM and Loechler EL: Environmental and occupational causes of cancer: New evidence 2005-2007. Rev Environ Health 23: 1-37, 2008.
21. Del Pup L, Mantovani A, Luce A, Cavaliere C, Facchini G, Di Francia R, Caraglia M and Berretta M: Endocrine disruptors and female cancer: Informing the patients (Review). Oncol Rep 34: 3-11, 2015.
22. Colosio C, Rubino FM, Alegakis A, Ariano E, Brambilla G, Mandic-Rajcevic S, Metruccio F, Minoia C, Moretto A, Somaruga C, *et al*: Integration of biological monitoring, environmental monitoring and computational modelling into the interpretation of pesticide exposure data: Introduction to a proposed approach. Toxicol Lett 213: 49-56, 2012.
23. Rubino FM, Mandic-Rajcevic S, Ariano E, Alegakis A, Bogni M, Brambilla G, De Paschale G, Firmi A, Minoia C, Micoli G, *et al*: Farmers' exposure to herbicides in North Italy: Assessment under real-life conditions in small-size rice and corn farms. Toxicol Lett 210: 189-197, 2012.
24. Montgomery MP, Kamel F, Saldana TM, Alavanja MC and Sandler DP: Incident diabetes and pesticide exposure among licensed pesticide applicators: Agricultural Health Study, 1993-2003. Am J Epidemiol 167: 1235-1246, 2008.
25. Starling AP, Umbach DM, Kamel F, Long S, Sandler DP and Hoppin JA: Pesticide use and incident diabetes among wives of farmers in the Agricultural Health Study. Occup Environ Med 71: 629-635, 2014.
26. Jaacks LM and Staimez LR: Association of persistent organic pollutants and non-persistent pesticides with diabetes and diabetes-related health outcomes in Asia: A systematic review. Environ Int 76: 57-70, 2015.
27. Reynolds LP and Caton JS: Role of the pre- and post-natal environment in developmental programming of health and productivity. Mol Cell Endocrinol 354: 54-59, 2012.
28. Tsimbiri PF, Moturi WN, Sawe J, Henley P and Bend JR: Health impact of pesticides on residents and horticultural workers in the Lake Naivash region, Kenya. Occup Dis Environ Med 3: 24-34, 2015.
29. Weichenthal S, Villeneuve PJ, Burnett RT, van Donkelaar A, Martin RV, Jones RR, DellaValle CT, Sandler DP, Ward MH and Hoppin JA: Long-term exposure to fine particulate matter: Association with nonaccidental and cardiovascular mortality in the agricultural health study cohort. Environ Health Perspect 122: 609-615, 2014.
30. Parkinson J: An essay on the shaking palsy. 1817. J Neuropsychiatry Clin Neurosci 14: 223-236, 2002.
31. Freire C and Koifman S: Pesticide exposure and Parkinson's disease: Epidemiological evidence of association. Neurotoxicology 33: 947-971, 2012.
32. Van Maele-Fabry G, Hoet P, Vilain F and Lison D: Occupational exposure to pesticides and Parkinson's disease: A systematic review and meta-analysis of cohort studies. Environ Int 46: 30-43, 2012.
33. Corsini E, Sokooti M, Galli CL, Moretto A and Colosio C: Pesticide induced immunotoxicity in humans: A comprehensive review of the existing evidence. Toxicology 307: 123-135, 2013.
34. Teng MW, Galon J, Fridman WH and Smyth MJ: From mice to humans: Developments in cancer immunoediting. J Clin Invest 125: 3338-3346, 2015.
35. Dunn GP, Old LJ and Schreiber RD: The three Es of cancer immunoediting. Annu Rev Immunol 22: 329-360, 2004.

36. Cassidy RA, Natarajan S and Vaughan GM: The link between the insecticide heptachlor epoxide, estradiol, and breast cancer. Breast Cancer Res Treat 90: 55-64, 2005.
37. Lee WJ, Blair A, Hoppin JA, Lubin JH, Rusiecki JA, Sandler DP, Dosemeci M and Alavanja MC: Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study. J Natl Cancer Inst 96: 1781-1789, 2004.
38. Lee WJ, Sandler DP, Blair A, Samanic C, Cross AJ and Alavanja MC: Pesticide use and colorectal cancer risk in the Agricultural Health Study. Int J Cancer 121: 339-346, 2007.
39. Weichenthal S, Moase C and Chan P: A review of pesticide exposure and cancer incidence in the agricultural health study cohort. Cien Saude Colet 17: 255-270, 2012.
40. Sifaki Pistolla D, Karageorgos SA, Koulentaki M, Samonakis D, Stratakou S, Digenakis E and Kouroumalis E: Geoepidemiology of hepatocellular carcinoma in the island of Crete, Greece. A possible role of pesticides. Liver Int 36: 588-594, 2016.
41. Bahadar H, Mostafalou S and Abdollahi M: Current understandings and perspectives on non-cancer health effects of benzene: A global concern. Toxicol Appl Pharmacol 276: 83-94, 2014.
42. Collins JJ, Ireland B, Buckley CF and Shepperly D: Lymphohaematopoeitic cancer mortality among workers with benzene exposure. Occup Environ Med 60: 676-679, 2003.
43. Snyder R: Leukemia and benzene. Int J Environ Res Public Health 9: 2875-2893, 2012.
44. Winek CL and Collom WD: Benzene and toluene fatalities. J Occup Med 13: 259-261, 1971.
45. Smith MT: Advances in understanding benzene health effects and susceptibility. Annu Rev Public Health 31: 133-148, 2010.
46. Uzma N, Kumar BS and Hazari MA: Exposure to benzene induces oxidative stress, alters the immune response and expression of p53 in gasoline filling workers. Am J Ind Med 53: 1264-1270, 2010.
47. Kanada M, Miyagawa M, Sato M, Hasegawa H and Honma T: Neurochemical profile of effects of 28 neurotoxic chemicals on the central nervous system in rats. Effects of oral administration on brain contents of biogenic amines and metabolites. Ind Health 32: 145-164, 1994.
48. Occupational exposures in petroleum refining; crude oil and major petroleum fuels. IARC working group on the evaluation of carcinogenic risks to humans. IARC Monogr Eval Carcinog Risks Hum 45: 1-322, 1989.
49. Reutman SR, LeMasters GK, Knecht EA, Shukla R, Lockey JE, Burroughs GE and Kesner JS: Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures. Environ Health Perspect 110: 805-811, 2002.
50. Marchetti F, Eskenazi B, Weldon RH, Li G, Zhang L, Rappaport SM, Schmid TE, Xing C, Kurtovich E and Wyrobek AJ: Occupational exposure to benzene and chromosomal structural aberrations in the sperm of Chinese men. Environ Health Perspect 120: 229-234, 2012.
51. Bennett LM and Davis BJ: Identification of mammary carcinogens in rodent bioassays. Environ Mol Mutagen 39: 150-157, 2002.
52. Rudel RA, Attfield KR, Schifano JN and Brody JG: Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. Cancer 109: 2635-2666, 2007.
53. Fenga C: Occupational exposure and risk of breast cancer. Biomed Rep 4: 282-292, 2016.
54. Collingwood KW, Raabe GK and Wong O: An updated cohort mortality study of workers at a northeastern United States petroleum refinery. Int Arch Occup Environ Health 68: 277-288, 1996, doi:10.1007/BF00409412.
55. Fu H, Demers PA, Costantini AS, Winter P, Colin D, Kogevinas M and Boffetta P: Cancer mortality among shoe manufacturing workers: An analysis of two cohorts. Occup Environ Med 53: 394-398, 1996.
56. Gérin M, Siemiatycki J, Désy M and Krewski D: Associations between several sites of cancer and occupational exposure to benzene, toluene, xylene, and styrene: Results of a case control study in Montreal. Am J Ind Med 34: 144-156, 1998.
57. Lewis RJ, Schnatter AR, Drummond I, Murray N, Thompson FS, Katz AM, Jorgensen G, Nicolich MJ, Dahlman D and Thériault G: Mortality and cancer morbidity in a cohort of Canadian petroleum workers. Occup Environ Med 60: 918-928, 2003.
58. Snyder R, Witz G and Goldstein BD: The toxicology of benzene. Environ Health Perspect 100: 293-306, 1993.
59. Bahadar H, Maqbool F, Mostafalou S, Baeeri M, Gholami M, Ghafour-Boroujerdi E and Abdollahi M: The molecular mechanisms of liver and islets of Langerhans toxicity by benzene and its metabolite hydroquinone in vivo and in vitro. Toxicol Mech Methods 25: 628-636, 2015.
60. Sun R, Cao M, Zhang J, Yang W, Wei H, Meng X, Yin L and Pu Y: Benzene exposure alters expression of enzymes involved in fatty acid β-oxidation in male C3H/He mice. Int J Environ Res Public Health 13: E1068, 2016.
61. Fenga C, Gangemi S, Giambò F, Tsitsimpikou C, Golokhvast K, Tsatsakis A and Costa C: Low-dose occupational exposure to benzene and signal transduction pathways involved in the regulation of cellular response to oxidative stress. Life Sci 147: 67-70, 2016.
62. Costa C, Ozcagli E, Gangemi S, Schembri F, Giambò F, Androutsopoulos V, Tsatsakis A and Fenga C: Molecular biomarkers of oxidative stress and role of dietary factors in gasoline station attendants. Food Chem Toxicol 90: 30-35, 2016.
63. Xia B, Chen K, Lv Y, Huang D, Liu J, Liang G, Zhang L, Wang F, Su C, Zou Y and Yang X: Increased oxidative stress and plasma Hsp70 levels among gasoline filling station attendants. Toxicol Ind Health 33: 171-181, 2017.