CRI/ICEIT
NEWSLETTER

VOL. 31 NO. 1 – January 2021
ISSN 0858-2793
BANGKOK, THAILAND

Chulabhorn Research Institute

INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

CRI's ICEIT has been designated as a
"UNEP Centre of Excellence for Environmental and Industrial Toxicology".

Human Health and Ocean Pollution

Ocean pollution is widespread, worsening, and poorly controlled. It involves a complex mixture of toxic metals, plastics, manufactured chemicals, petroleum, urban and industrial wastes, pesticides, fertilizers, pharmaceutical chemicals, agricultural runoff, and sewage. More than 80% of this pollution arises from land-based sources. It reaches the oceans through rivers, runoff, atmospheric deposition and direct discharges.

The report on "**Human Health and Ocean Pollution**" presents a broad and comprehensive examination of the multiple dangers to human health and the environment posed by pollution of the seas.

The report covers (1) the damage done to developing brains of infants by marine mercury pollution; (2) the deleterious impacts of ocean acidification on coral reefs, shellfish, and calcium-containing micro-organisms at the base of the marine food web; and (3) new data on the toxicity of microplastics and nanoplastics.

Specifically, petroleum-based pollutants reduce photosynthesis in oxygen-producing marine microorganisms. Carbon dioxide absorption causes ocean acidification. Plastic pollution threatens marine mammals, fish and seabirds, and breaks down into microplastic and nanoplastic particles that can enter the tissues of marine organisms that can eventually be consumed by humans.

Methylmercury and polychlorinated biphenyls (PCBs) pollution in seafood can damage children's developing brains, reduce IQ and increase children's risks for autism, attention deficit/hyperactivity disorder (ADHD) and learning disorders. Adult exposures to methylmercury increase risks for cardiovascular disease and dementia. Manufactured chemicals in seafood, phthalates, bisphenol A, flame retardants, and perfluorinated chemicals, can disrupt endocrine signaling, reduce male fertility, and increase the risk of cancer.

Harmful Algal Blooms (HABs) produce potent toxins that accumulate in fish and shellfish and cause severe neurological impairment and rapid death.

Yet, despite all these issues of concern, the study finds that ocean pollution and its harmful effects can be controlled and prevented.

Data-driven strategies targeting major pollution sources have been highly effective in reducing marine pollution, including that caused by mercury, persistent organic pollutants, sewage, and agricultural runoff. These successes have boosted economies, increased tourism, helped restore fisheries, and improved human health and well-being.

The report makes a series of urgent recommendations including eliminating coal combustion, banning all uses of mercury, banning single-use plastics, controlling coastal discharges, and reducing applications of chemical pesticides and fertilizers.

It also calls for robust monitoring of all forms of ocean pollution, and the designation of large, new marine protected areas to safeguard critical ecosystems, protect vulnerable fish stocks, and enhance human health and well-being.

Most importantly, the report calls for a global recognition of the gravity of ocean pollution, the acknowledgement of its impacts on human health and the environment, and the need for evidence-based action to stop the problem at its source.

Source: Annals of Global Health. Vol. 86, Issue 1, Article 151, December 2020.

Is Obesity the Missing Link between COVID-19 Severity and Air Pollution?

Air-quality data from up to 71 Italian provinces have been shown to significantly correlate with cases of Coronavirus Disease 19 (COVID-19). If atmospheric particulate matter can act as a carrier, facilitating the transport and spread of many chemical and biological contaminants, including viruses, then chronic exposure to atmospheric contamination may have played a role in facilitating the spread of COVID-19.

A previous study hypothesized that the particularly lethal effects of the novel Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) in Northern Italy might have been explained, at least in part, by the evidence of record high levels of pollution reported in this area. Severe COVID-19 and smog exposure are known to hyperactivate the immune system with subsequent lung inflammation and injury.

This hypothesis alone does not fully explain why specific subgroups of subjects, such as elderly and obese patients, are at major risk of severe manifestation of COVID-19. However, researchers have hypothesized that obesity may be one of the links between COVID-19 severity and high levels of air pollution.

Obesity is known to be a predisposing factor for SARS-CoV-2 infection and worse COVID-19 outcomes. A growing body of evidence supports the hypothesis that there exists a mutual relationship between obesity, air pollution and lung inflammation.

Obesity may intensify the detrimental effects of air pollution since both these conditions share an excessive activation of the immune system and a lung inflammatory infiltrate.

In addition, fat mass excess has also been associated to increased pulmonary and systemic inflammation, similar to what happens in the lungs of subjects exposed to air pollutants and of patients diagnosed with COVID-19.

In conclusion, although many variables, such as age and health care policies must be taken into account in the analysis of the present pandemic, the observations outlines here suggest that obesity may act as an effect modifier of smog-induced lung-injury, and that the concomitant presence of obesity together with air pollution could better explain the higher virulence, faster spread and greater mortality of COVID-19 in Northern Italy compared to the rest of the country.

Source: Environmental Pollution, Vol. 266, Article 115327, November 2020.

Effects of Fetal Exposure to Phthalates and Bisphenols on Childhood Lipid and Glucose Metabolism

Endocrine-disrupting chemicals (EDCs), such as phthalates and bisphenols, are widely used in food packaging, household products and medical devices. Because they pass through the placenta, it is possible that phthalates and bisphenols may have effects on fetal life during that specific critical period of life.

Phthalates and bisphenols may affect fetal development by stimulating estrogen and inhibiting androgen receptors, activating peroxisome proliferator-activated receptors (PPARs) or retinoid X receptors (RXRs), and changing the fetal transcriptome.

Limited prospective studies on associations between fetal exposure to phthalates or bisphenols and metabolic diseases are available. They show no clear association of fetal exposure to phthalates or bisphenols with childhood lipid and glucose metabolism.

The present study hypothesizes that fetal exposure to phthalates and bisphenols leads to fetal metabolic adaptations, which then persistently affect glucose and lipid metabolism.

In this study, the sex-specific associations of maternal phthalate and bisphenol urine concentrations were assessed in the first, second and third trimesters of pregnancy. Non-fasting lipids, glucose and insulin concentrations in their children were then assessed at the age of 10 years.

The results showed that the third trimester maternal urine phthalic acid concentration was associated with higher triglyceride concentration among boys, while no association of fetal exposure to phthalates with other lipid concentrations during childhood was observed.

The second trimester maternal high molecular weight phthalates (HMWP) and di-2-ethylhexylphthalate (DEHP) urine concentrations were associated with lower glucose concentration among boys.

Maternal bisphenol urine concentrations showed no associations with lipid concentrations during childhood. The higher bisphenol F concentrations during pregnancy were associated with lower insulin concentrations among boys.

Both phthalates and bisphenol A influence epigenetic regulatory mechanisms, which may need considerable time to lead to measurable changes in circulating biomarkers. This timing issue could possibly explain the discrepancies. It has even been suggested that exposure to bisphenols influences health in subsequent generations.

The relationship between exposure to endocrine disruptors and metabolic disturbances is potentially sex-specific. This could be due to sex-specific differences in PPAR-activity of phthalates and the estrogenic effect of bisphenol A.

The results of the present study add to the growing body of evidence that fetal exposures of specific phthalates and bisphenols could influence later metabolic health in humans. Further studies are needed to elucidate the underlying mechanisms of endocrine disruptors on lipid and glucose metabolism in humans specifically.

Source: Environment International, Vol. 144, Article 106063, November 2020.

Mechanisms of Endocrine-disrupting Chemicals in Thyroid Diseases: The Epigenetic Way

Endocrine-disrupting chemicals (EDCs) have been defined by the U.S. Environmental Protection Agency (EPA) as "an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental processes".

Some EDCs are believed to specifically exert thyroid-disrupting effects. Thyroid hormones, which have varied and sometimes unexpected or pleiotropic effects, play a central role as regulators of metabolism, bone formation, myocardial contractility and neural growth and differentiation. They are also of special importance for fetal growth and differentiation.

Therefore, substances with disrupting effects for thyroid homeostasis represent a potential hazard to public health and an understanding of the mechanisms through which they can produce their negative effects is of outmost importance.

Recently, epigenetic changes have been suggested to be correlated with possibly deleterious effects leading to thyroid disorders in susceptible individuals.

Epigenetics refers to gene function alterations that are heritable but reversible and do not entail a modification in nucleotide sequence. The term also includes different processes such as DNA methylation, histone tail modification, and non-coding RNAs.

All mechanisms are strictly related as DNA methylation affects, histone modifications and vice versa, while non-coding RNAs, microRNAs and long non-coding RNAs strongly contribute to the regulation of gene expression as well as in shaping chromatin structures.

The importance of epigenetic control has been dramatically highlighted with the advent of high-throughput genomic technologies which revealed that: (i) only <3% of the mammalian genome is transcribed into protein-coding mRNAs, and even more importantly, (ii) the proportion of non-protein-coding DNA increases which are responsible for increasing developmental complexity.

This review focuses on three main classes of thyroid disorders that have been associated with EDC exposure: disruption of thyroid hormone balance *in utero*, thyroid cancers, and autoimmune thyroiditis.

The researchers also attempt to show the possible role played by epigenetic mechanisms which relate the exposure to toxic compounds and the onset and/or progression of thyroid disease.

Although direct and indirect evidence points to epigenetic changes as one of the likely mechanisms underlying the adverse health outcome of EDC exposure, there is currently no clear link between EDC-induced epigenetic change and a specific thyroid disease.

Large studies are also necessary to understand the impact of EDCs on epigenetics and, in turn, the influence of epigenetic mechanisms on endocrine function, keeping in mind that alterations of the thyroid homeostasis can also affect epigenetic signature.

The review begins with an analysis of epigenetic modifications associated with a specific thyroid disease and an overview of the EDCs implicated in triggering these diseases. The researchers attempt to summarize the sparse experimental evidence supporting the involvement of epigenetic mechanisms in EDC-induced thyroid disease.

Some epigenetic mechanisms appear conserved in different EDC-triggered thyroid diseases. This is true not only for global modification such as DNA methylation that is deeply affected by EDC exposure, but also for more specific mechanisms.

These observations suggest a possible scenario where chemical exposure induces epigenetic modification that can lead to different disease outcomes, depending on the time and length of exposure and/or the genetic susceptibility. The review reinforces the importance of an integrated view of the relationship between EDC exposure, genetic and epigenetic mechanisms, and health alterations.

Overall, the present review supports the hypothesis that epigenetic mechanisms could play an important role in determining thyroid diseases in response to environmental contaminants.

A complex and often inter-connected network of epigenetic modifications can be activated by a large number of widespread environmental contaminants.

The analysis clearly shows that further research in this field is still necessary to fully elucidate the relationships linking pollutants, epigenetic mechanisms and disease pathogenesis, and to exploit this knowledge for the development of new classes of diagnostic and prognostic tools for dealing with thyroid diseases.

Source: International Journal of Environmental Research and Public Health, Vol. 17, Issue 21, Article 7787, November 2020.

Effects of Cadmium, Lead, and Mercury on Reproductive Organs

Reproductive organs are essential not only for the life of an individual but also for the survival and development of the species.

The response of reproductive organs to toxic substances differs from that of other target organs, and they may serve as an ideal "barometer" for the deleterious effects of environmental pollution on animal and human health.

Impaired reproductive function is often related to environmental exposure to toxic substances, including toxic metals, especially cadmium, lead, and mercury, to which most populations are common exposed.

These metals are listed by the World Health Organization (WHO) as toxicants of major public health concern. Data from epidemiological studies have suggested that environmental exposure to cadmium, lead, and mercury may have produced reproductive and developmental toxicity.

Accordingly, researchers have been alerted to the search for evidence of reproductive toxicity induced by cadmium, lead, and mercury. The focus has been on changes in the structure and function of male and female reproductive organs of various animal species. Relevant human studies have also come under review.

The toxic mechanisms are described as ion mimicry, disruption of cell signaling pathways, oxidative stress, altered gene expression, epigenetic regulation of gene expression, apoptosis, disruption of the testis-blood barrier, inflammation, and endocrine disruption.

The experimental studies reviewed indicate that testis and ovary are particularly sensitive to cadmium, lead, and mercury because these organs are distinguished by intense cellular activity where vital processes of spermatogenesis, oogenesis, and folliculogenesis occur.

In their individual effects, the toxicity of cadmium, lead, and mercury in reproductive organs appear strikingly similar.

In ovaries, the most significant changes are decreased follicular growth, increased number of atretic follicles, degeneration of the corpus luteum, and prolonged and/or irregular cycle.

In testes, the most significant changes include disorganization of seminiferous tubules; alterations in spermatogenic cell arrangement; alterations in the basal membrane structure; abnormalities of the testicular stroma; decreased spermatozoa count, motility, and viability; and altered spermatozoa morphology.

These are signs of the adverse dose- and time-dependent effects of cadmium, lead, and mercury on the architecture of reproductive organs.

In general, toxic effects of various substances in reproductive organs occur at low concentrations. The toxic mechanisms of each of these metals have been established. Future research should be aimed elucidating the molecular mechanism(s) and action of these metals in combination to mimic human co-exposure situations.

In addition, strategies to prevent toxic exposure and the synergy of antagonistic interactions in the presence of more than one of these three metals should be examined in future research.

Source: Toxics, Vol. 8, Issue 4, Article 94, October 2020.

The Impact of Phthalates on Reproductive Health

There is an increasing worldwide trend towards reproductive disorders, such as hormone-dependent cancers, infertility, and decreased fecundity. One of the causes of this trend could be environmental chemicals such as phthalates.

Phthalates are ubiquitous chemicals used in the manufacture of the plasticizers which enable the elasticity of plastic products. Research has shown that exposure to phthalates is associated with various health issues, but most significantly with reproductive disorders.

The present review attempts to present an overview of the current body of knowledge concerning the impact of phthalates on reproductive health at multiple levels. This review integrates the results from *in silico*, *in vitro*, *in vivo* and epidemiological studies to show the complexity of effects phthalates that bring about in reproductive disorders.

The review summarizes the knowledge of general reproductive regulators, phthalate toxicity and the effect of phthalates on male and female reproduction at clinical, hormonal, and intracellular levels.

Prenatal and postnatal exposure to phthalates induces a wide spectrum of reproductive disorders. Phthalates may induce alterations in puberty, in the development of testicular dysgenesis syndrome, in cancer, and in fertility disorders in both males and females.

In males, phthalates can induce testicular dysgenesis syndrome (TDS), which is connected with impaired spermatogenesis.

In females, the exposure to phthalates can induce premature ovarian failure (POF), which is linked with impaired oogenesis and folliculogenesis.

These reproductive disorders are mainly associated with a disrupted hypothalamic-pituitary-gonadal (HPG) axis that affects the process of steroidogenesis in males as well as females.

At the hormonal level, phthalates interact with HPG axis activity, which is

(Continued on page 5)

Organophosphate Pesticide Exposure and Breast Cancer Risk

Organophosphate pesticides (OPs) are currently one of the most commonly used classes of insecticides in the United States and are applied in agricultural, residential, and community settings. Metabolites of OPs have been detected in the urine of >75% of the U.S. population.

While studies have shown that OP exposure is associated with risk of neurological disease and some cancers, the relationship between OP exposure and breast cancer risk is not well understood.

After skin cancer, breast cancer is the most common type of cancer among women worldwide. Approximately one in eight women will be diagnosed with invasive breast cancer in their lifetime. As studies have suggested that only 5-10% of breast cancer cases are hereditary, the impact of lifestyle and environmental factors takes on greater significance.

A recent study has found that a high consumption of organic foods (i.e. pesticide free) correlates with a decreased risk of postmenopausal breast cancer.

Given the widespread exposure to OPs and the high number of breast cancer cases, it is important to examine the relationship between OP exposure and breast cancer risk.

Among the limited studies on OP exposure and human breast cancer risk, many have demonstrated the effect of OP exposure on mammary carcinogenesis in both animal and cell models.

The present review highlights the existing literature on human, animal, and cell-based studies examining the relationships between OPs that are currently being used and breast cancer risk.

Since breast development is controlled by the endocrine system, endocrine disruption, defined as any disruption in the normal activity of the endocrine system, can lead to altered breast development and may increase breast cancer risk.

Some studies in human subjects positively associated malathion, terbufos, and chlorpyrifos with human breast cancer risk. Some laboratory studies have demonstrated that malathion and chlorpyrifos have estrogenic potential and other cancer-promoting properties.

Most of the studies suggested that malathion and chlorpyrifos are potential estrogen agonists and thus may activate the estrogen receptor α (ERα) and aryl hydrocarbon receptor (AhR) pathway, leading to cellular proliferation and other mammary cell disruptions.

In addition to acting as acetyl-cholinesterase inhibitors, evidence suggests that malathion and chlorpyrifos have the potential to cause endocrine disruption, induce oxidative stress, and alter the expression of cell cycle proteins and cell adhesion molecules important for breast development.

However, while treatment with malathion resulted in increased cell proliferation, treatment of chlorpyrifos resulted in either increased cell proliferation or cell cycle arrest and apoptosis, perhaps depending on the dosage administered.

The findings of this rapid review on human, animal, and cell-based studies suggest that certain OPs may be involved in increasing breast cancer risk. These OPs can potentially increase breast cancer risk through various mechanisms including increased oxidative stress, disruption of adhesion molecules, acetylcholinesterase inhibition, endocrine disruption, and induction of genomic instability.

However, the human studies were limited in number. Most included agricultural settings in several geographical areas in the U.S. and did not address cumulative exposure.

Taken together and given the prevalence of OPs and number of breast cancer cases, there is a need for further research on human subjects in non-occupational settings, potentially including the assessment of cumulative lifetime exposure to OPs, biomonitoring, mortality data, and a wider geographical assessment.

Source: International Journal of Environmental Research and Public Health, Vol. 17, No. 14, Article 5030, September 2020.

The Impact of Phthalates on Reproductive Health

(Continued from page 4)

crucial for proper reproductive development during prenatal and postnatal periods. If levels of sex hormones are insufficient or excessive, reproductive disorders may occur.

At the intracellular level, phthalates can interfere with nuclear receptors, membrane receptors, and intracellular signaling pathways, and can also modulate gene expression associated with reproduction.

The results of this review suggest that the reproductive disorders associated with phthalate exposure can have potential transgenerational or multigenerational effects. The increased use of phthalates and other endocrine disruptors in the plastic products industry in the last 70 years can explain the worldwide higher prevalence of reproductive disorders.

It will be vital to conduct more epidemiological and experimental studies to understand if and how phthalates can induce cancer in male reproductive organs.

The expansion of current knowledge on the expression, effects, and intracellular mechanisms of phthalates on male and female HPG systems is necessary for the efficient prevention and treatment of their adverse influence on human and animal reproduction.

Source: International Journal of Environmental Research and Public Health, Vol. 17, No. 18, Article 6811, September 2020.

ATSDR: Toxicological Profile for Lead

Final toxicological profile for lead is now available from the Agency for Toxic Substances and Disease Registry (ATSDR) of the U.S. Department of Health and Human Services.

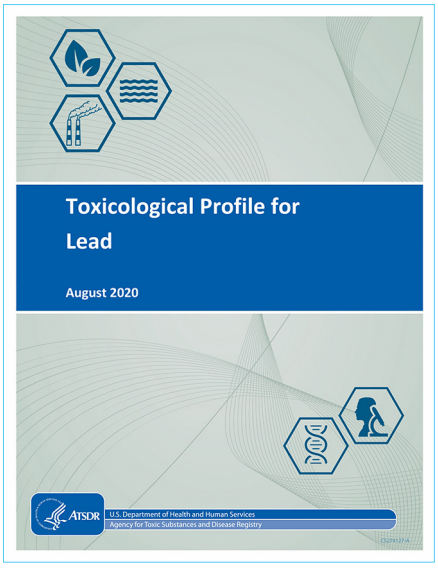
The ATSDR toxicological profile succinctly characterizes the toxicology and adverse health effects information for the toxic substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicological properties.

According to ATSDR, the general population is primarily exposed to lead via the oral route, with some contribution from the inhalation route. The agency notes that inhalation exposures can be more important in occupational settings, depending on particle size. Occupational exposure to organic lead compounds may also involve dermal absorption.

The ATSDR profile for lead does not attempt to separate health effects according to exposure route because the primary systemic toxic effects of lead are the same, regardless of the route of entry into the body.

More information on ATSDR's toxicological profiles, including a full list of substances with published profiles, is available on the website - https://www.atsdr.cdc.gov/toxprofiledocs/index.html.

Source: Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Lead. August 2020.



Toxic Metal Exposure as a Possible Risk Factor for COVID-19 and Other Respiratory Infectious Diseases

The highly infectious coronavirus disease 2019 (COVID-19) is due to infection by the coronavirus SARS-CoV-2 first spotted in October 2019, causing a massive outbreak in December 2019.

The new virus predominantly affects the respiratory system, causing COVID-19 pneumonia. Other systems are also involved in the infection, especially in severe cases where there is often a vascular and cytokine storm resulting in systemic inflammation.

The clinical course of COVID-19 is highly variable. It is characterized by high numbers of asymptomatic and mild cases, but it frequently also progresses to pneumonia, acute respiratory distress syndrome (ARDS) and organ dysfunction. At present, the particular causes of such clinical heterogeneity are unclear.

In parallel with the search for therapeutic approaches for healing and recovery, an estimation of the potential risk factors is also essential for controlling the spread of the disease and reducing the risk of infection.

Multiple medical, lifestyle, and environmental conditions, including smoking and particulate pollution, have been put forward as risk factors for COVID-19 susceptibility and severity.

Toxic metals are present as effector agents in tobacco smoke and particulate pollution, and are known to have respiratory, immunotoxic, and proinflammatory effects. Researchers have therefore been proposing that toxic metal exposure may also be considered as a potential risk factor for COVID-19 severity.

Therefore, the objective of the study was to review recent data on the role of toxic metal exposure in the development of respiratory dysfunction and immunotoxicity. The compromising role of metal toxicity in viral diseases has been noted in epidemiological and experimental studies. They point to potential crossroads between heavy metal exposure and COVID-19 severity risk.

The existing data demonstrate that arsenic, cadmium, lead, and mercury exposure is associated with respiratory dysfunction and respiratory disease including chronic obstructive pulmonary disease (COPD).

These observations corroborate laboratory findings on the role of heavy metal exposure in impaired mucociliary clearance, reduced barrier function, airway inflammation, oxidative stress, and apoptosis.

Both clinical and laboratory studies have shown the association between heavy metal exposure and severity of viral diseases, including influenza and respiratory syncytial virus. The latter may be considered a consequence of the adverse effects of metal exposure on adaptive immunity.

Although data directly linking heavy metal exposure and COVID-19 risk and/or severity are lacking, there is still reason to urge reduction in heavy metal emissions as a step which could

(Continued on page 7)

Associations between Lead Exposure and Immune Responses in Preschool Children

Lead (Pb) ranks the second in priority in the Agency for Toxic Substances and Disease Registry (ATSDR), based on a comprehensive assessment of their frequency of exposure to humans, toxicity, and human exposure probability (ATSDR, 2020).

The general population risk exposure to lead in the air, food and drinking water. Women in particular can also be exposed to lead in cosmetics.

Lead exposure in daily life has become a serious public health issue. Lead produces potential health threats by accumulating in the human body over time, impairing multiple organ systems, and causing adverse health effects.

Studies have shown that lead exposure affects immune functions, but few studies have examined the relationships between *in utero* lead exposure, a sensitive period for immune development, and later immune responses.

There have also been relatively few studies investigating associations between prenatal exposure to lead and immune responses biomarkers in children.

Gestation is a critical period in the development of fetal immune system, making it particularly sensitive to environmental toxicants. Prenatal environmental exposure may affect immune development, altering postnatal immune responses and cytokine profiles, and contributing to an increased risk of childhood and later-life infectious and allergic disorders.

Since lead can readily cross the placenta from the mother to the growing fetus, the effects of prenatal lead exposure on childhood immune function cannot be ignored. Assessment of prenatal lead exposure levels in urine, a valid biomarker showing a very high correlation with blood lead, can be used as an alternative to fetal exposure.

To investigate the effects of prenatal and childhood lead exposure on the immune responses of preschool-aged children, a prospective birth cohort study was established in Wuhan, China, in which lead concentrations were analyzed in maternal urine during the third trimester and in plasma samples from children aged about 3 years.

The researchers assessed immune responses by measuring immune cytokines in the children's plasma and peripheral blood T lymphocyte subsets at 3 years of age. Each unit increase in maternal urinary lead concentration (μg/g creatinine) was associated with reduced Interleukin-10 (IL-10) and reduced IL-4 levels.

Lead concentration in children's peripheral blood is considered as a good biomarker of postnatal exposure.

The present study found that tumor necrosis factor alpha (TNF-α) was positively associated with lead levels in children's plasma, and increased TNF-α was observed in boys in the gender stratification analysis.

TNF-α protein secretion was produced primarily by activated macrophages and lymphocytes in an inflammatory infection status. It is especially noted that soluble, biologically active TNF-α plays an important role in the inflammatory responses.

With the except of TNF-α, this study did not find any relationships between childhood lead exposure and changes in other cytokines or T lymphocyte subsets. This result may be related to differences in lead exposure levels and the research populations in different studies.

In conclusion, the study showed that prenatal lead exposure was associated with reduced IL-10 and IL-4 cytokines, while childhood lead exposure was associated with increasedTNF-α

This prospective cohort study integrated prenatal and postnatal exposure, as well as contemporaneous analysis of cytokines and lymphocyte subsets in children. It provides new evidence for understanding the effect of lead exposure on the children immune responses of preschool children.

Further research is needed to confirm these findings and to clarify the impacts of lead exposure early in life on children's immune responses.

Source: Ecotoxicology and Environmental Safety, Vol. 207, Article 111536, January 2021.

Toxic Metal Exposure as a Possible Risk Factor for COVID-19 and Other Respiratory Infectious Diseases

(Continued from page 6)

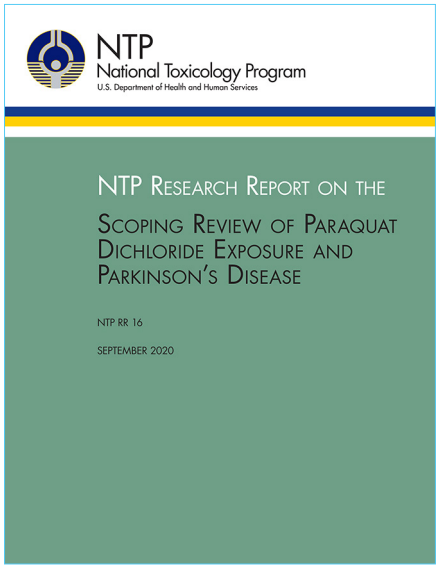
significantly reduce lung immuno-pathology and inflammation, both of which are known to increase the risk of viral and bacterial respiratory disease.

In addition, individuals can take the initiative to avoid heavy metal exposure by using protective masks or portable air filters, especially in highly-polluted urban environments. In this way, proactive individualy can contribute to reducing of risk of infection and its severity.

The use of zinc, selenium, or other functional antagonists of heavy metals may also prevent adverse effects of heavy metals on respiratory and immune systems. At the same time, both epidemiological and laboratory studies are urgently required to more accurately and usefully characterize the direct association between heavy metal exposure, COVID-19 risk, and pathogenetic mechanisms.

Source: Food and Chemical Toxicology, Vol. 146, Article 111809, December 2020.

NTP Research Report: Scoping Review of Paraquat Dichloride Exposure and Parkinson's Disease



Paraquat dichloride (commonly referred to as paraquat) is a restricted-use, broad-spectrum herbicide that is commonly used in the United States to control weeds in agricultural and horticultural crops.

Because paraquat is not registered for home use, the highest exposures would likely occur among persons directly involved in manufacturing or applying paraquat, or to those living on or near farms or other areas where paraquat is being manufactured or applied.

Observational studies of people who apply pesticides and data from experimental animal studies indicate that long-term, chronic exposure to paraquat may lead to central nervous system toxicity.

While performing scoping activities to classify environmental exposures associated with Parkinson's disease, the National Toxicology Program (NTP) identified paraquat as a potential candidate for systematic review.

Subsequently, the NTP became aware that the Office of Pesticide Programs (OPP) of the U.S. Environmental Protection Agency (EPA) was also evaluating paraquat as part of registration review activities. The NTP therefore collaborated with the EPA in order to avoid duplication of effort.

The objective of these scoping activities was to identify and characterize peer-reviewed, published scientific literature relevant to paraquat exposure as well as neurobehavioral and neuropathological endpoints associated with Parkinson's disease in humans and related models in experimental animals or *in vitro* studies.

Using systematic review methodologies, NTP developed a scoping review and evidence maps of published scientific literature to support potential follow-up systematic review and to identify extant research gaps.

The evidence maps are interactive, sortable visualizations of quantitative data from epidemiological studies and experimental study characteristics with links to publications.

A considerable body of evidence was identified as relevant to paraquat exposure and Parkinson's disease that can be used in developing future systematic reviews as were data gaps and scientific challenges that could be addressed by future research.

Future epidemiological study could include biomonitoring of specific pesticide exposures to separate paraquat's effects from those of other chemicals and mixtures.

Inclusion of higher numbers from the general population of paraquat-exposed and incident Parkinson's disease cases, including women exposed to paraquat and/or with symptoms of Parkinson's disease, would allow findings to be further generalized beyond occupational settings.

To increase the direct relevance of experimental animal studies to Parkinson's disease in humans, future laboratory animal studies could include administration of paraquat via a route that is more relevant to the general human population (oral or inhalation), measurement of neuromuscular or neurobehavioral endpoints, and direct counts of dopaminergic neurons.

Investigating the effects of longer-term paraquat exposures *in vitro* on endpoints with clear linkages to Parkinson's disease (such as loss in neuron numbers and accumulation of α-synuclein) in primary human cell models might provide critical mechanistic information linking these exposures to neurological deficits observed in humans and animals.

Source: National Toxicology Program (NTP) Research Report 16, September 2020.

The ICEIT NEWSLETTER is published quarterly by the International Centre for Environmental and Industrial Toxicology of the Chulabhorn Research Institute. It is intended to be a source of information to create awareness of the problems caused by chemicals. However, the contents and views expressed in this newsletter do not necessarily represent the policies of ICEIT.

Correspondence should be addressed to:

ICEIT NEWSLETTER
Chulabhorn Research Institute
Office of Academic Affairs
54 Kamphaeng Phet 6 Road
Lak Si, Bangkok 10210, Thailand
Tel: +66 2 553 8535
Fax: +66 2 553 8536
CRI Homepage: <http://www.cri.or.th>

For back issues of our newsletter, please visit:

http://www.cri.or.th/en/envtox/et_newsletter.htm