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Carbon Disulfide (CS_2) Interference in Glucose Metabolism from Unconventional Oil and Gas Extraction and Processing Emissions

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ABSTRACT: Carbon disulfide (CS_2) has been historically associated with the manufacturing of rayon, cellophane, and carbon tetrachloride production. This study is one of the first to identify elevated atmospheric levels of CS_2 above national background levels and its mechanisms to dysregulate normal glucose metabolism. Interference in glucose metabolism can indirectly cause other complications (diabetes, neurodegenerative disease, and retinopathy), which may be preventable if proper precautions are taken. Rich et al found CS_2 and 12 associated sulfide compounds present in the atmosphere in residential areas where unconventional shale oil and gas extraction and processing operations were occurring. Ambient atmospheric concentrations of CS_2 ranged from 0.7 parts per billion by volume (ppbv) to 103 ppbv over a continuous 24-hour monitoring period. One-hour ambient atmospheric concentrations ranged from 3.4 ppbv to 504.6 ppbv. Using the U.S. Environmental Protection Agency Urban Air Toxic Monitoring Program study as a baseline comparison for atmospheric CS_2 concentrations found in this study, it was determined that CS_2 atmospheric levels were consistently elevated in areas where unconventional oil and gas extraction and processing occurred. The mechanisms by which CS_2 interferes in normal glucose metabolism by dysregulation of the tryptophan metabolism pathway are presented in this study. The literature review found an increased potential for alteration of normal glucose metabolism in viscose rayon occupational workers exposed to CS_2. Occupational workers in the energy extraction industry exposed to CS_2 and other sulfide compounds may have an increased potential for glucose metabolism interference, which has been an indicator for diabetogenic effect and other related health impacts. The recommendation of this study is for implementation of regular monitoring of blood glucose levels in CS_2-exposed populations as a preventative health measure.

KEYWORDS: natural gas, carbon disulfide, glucose metabolism, tryptophan pathway, diabetes, unconventional shale

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Introduction

Exposure to carbon disulfide (CS_2) has historically been associated with the manufacturing of rayon, cellophane, and carbon tetrachloride production.[1] With the migration of the garment industry overseas, CS_2 emissions in the United States has been in decline. Knowledge of the detrimental effect CS_2 can have on the neurological, respiratory, and cardiovascular systems has become lost over time and until now considered only to be occupationally related. In the 1990s, technological advancements in horizontal drilling and hydraulic fracturing established a feasible and economic way to extract oil, natural gas (NG), and natural gas liquids from unconventional shale geologic formations, many of which lie beneath urban cities. Although these techniques enable minimal surface disruption, they may inadvertently expose residential communities to high levels of industrial chemicals, including CS_2, present in emissions associated with unconventional oil and gas (UOG) extraction and processing.

The Barnett Shale geologic formation lies beneath highly populated urban and suburban areas in North Texas and was one of the first places to be developed by *urban drilling*.[2] Recent air monitoring studies in the Barnett Shale found elevated atmospheric concentrations of CS_2 and associated sulfide compounds in and around residential areas where UOG extraction and processing operations were occurring.[3–5] Rich et al found ambient atmospheric concentrations of CS_2 in residential areas ranging from 0.7 parts per billion by volume (ppbv) to 103 ppbv over a continuous 24-hour monitoring period (Table 1). One-hour ambient atmospheric concentrations ranged from 3.4 ppbv to 504.6 ppbv.[4]

To determine if CS_2 levels were elevated regionally by UOG activities, atmospheric chemical concentrations in this study were then compared to the U.S. Environmental Protection Agency (EPA) Urban Air Toxics Monitoring Program (UATMP).[6] The UATMP is the most comprehensive monitoring program in the U.S. and includes

Table 1. CS_2 and associated sulfide compounds in NG emissions: 24-hour minimum and maximum concentrations in ppbv.

CAS#	CHEMICAL	MIN (ppbv)	MAX (ppbv)	MEDIAN (ppbv)	MEAN (ppbv)	SD	#ND
75150	Carbon disulfide	0.7	103	4	11.75	20.5	22
624920	Dimethyl disulfide	0.3	200	1.93	15	31.56	29
20333395	Methyl ethyl disulphide	0.3	145	1.78	11.18	24.27	31
3658808	Dimethyl trisulfide	1.2	46.3	1.52	8.02	14.86	37
463581	Carbonyl sulfide	0.3	36.7	1.41	4.22	7.1	40
110816	Diethyl disulfide	0.3	32.7	1.5	3.15	5.92	43
226666	Diethyl trisulfide	0.3	8.23	1.41	2.14	1.62	43
53966362	Ethyl, methylethyl disulfide	0.3	46.7	1.4	3.68	8.87	46
30453317	Ethyl n-propyl disulfide	0.3	25.2	1.4	2.25	3.48	48
2179604	Methyl propyl disulfide	0.3	41.6	4.1	2.59	5.71	49
60779240	Methyl n-butyl disulfide	0.3	15.5	1.4	1.92	2.1	49
72437640	Propyl n-butyl disulfide	0.3	14.6	1.4	1.9	1.98	49
629196	Dipropyl disulfide	0.3	23.1	1.4	2.07	3.11	49

urban, suburban, rural, and industrial locations across the U.S. CS_2 was the only sulfide compound that could be evaluated in the UATMP study; its collection procedures did not include other sulfide compounds. Years 2007–2012 were included for a comprehensive evaluation of atmospheric conditions over time. The comparison values are presented in Table 2.

When comparing CS_2 atmospheric concentrations present in the residential areas of the Barnett Shale to those in the UATMP study, results indicate that atmospheric CS_2 concentrations in this study exceeded the national maximum average by 61% (2007), 94% (2008–2009), 53,268% (2010), 351% (2011), and 535% (2012). Atmospheric CS_2 levels in this study appeared to have greater variability (SD, 20.50) when compared to background CS_2 levels in the UATMP study. The elevated atmospheric concentrations of CS_2 in the Barnett Shale area may reflect the contribution of CS_2 from emissions produced during specific phases in UOG activity or production.

CS_2 levels in the atmosphere were found to be diurnally variable and corresponded to the distance from the emission source. Atmospheric half-life of CS_2 ranges from 8 days to 12 days due to its ability to react with OH radicals in the atmosphere.[7] Therefore, CS_2 has the capacity to travel long distance in the atmosphere and affect air quality regionally as well as locally.

Complaints of adverse health effects related to UOG emissions were found to be consistent with CS_2 exposure.[7] However, air monitoring analysis found multiple volatile organic compounds present simultaneously with CS_2 and sulfide chemicals; therefore, it is difficult to determine which chemical or chemicals were the initiator of the health complaints.

Literature Review Results

A study by Ruijten et al supported the potential for adverse health effects and determined that even low-level CS_2 exposure could interfere with normal metabolic processes. Their research found that exposed individuals may be asymptomatic for a period of time, while changes occurred at a molecular level.[8] A study by Franco et al showed a positive correlation between CS_2 and latent diabetes in viscose rayon workers.[9] The mechanism of toxicity and magnitude of health impact were

Table 2. CS_2 ambient atmospheric concentrations in comparison to the U.S. EPA National Monitoring Programs Annual Report (2007–2012).

	MIN (ppbv)	MAX (ppbv)	MEDIAN (ppbv)	MEAN (ppbv)	SD	# DETECTS
Study results	0.700	103.00	4.00	11.750	20.500	28.00
UATMP 2007	0.005	64.10	0.442	1.982	4.826	1252
UATMP 2008–09	0.002	53.00	0.040	1.400	3.940	1820
UATMP 2010	0.005	0.193	0.102	0.999	0.025	1258
UATMP 2011	0.004	22.80	0.003	0.925	2.600	1219
UATMP 2012	0.004	16.20	0.021	0.669	0.197	1408

found to be irrespective of industry, but rather depended on the concentration, frequency, and duration of CS_2 exposure. UOG workers exposed to CS_2 may experience similar health effects, as seen in viscose rayon industry workers.[10] Recent research has associated exposure to CS_2 to other health effects involving endocrine regulation, bone metabolism, cardiovascular function, and neurodegenerative disease, including Alzheimer's disease and aging.[11,12]

As energy extraction expands across the United States, atmospheric levels of CS_2 and associated sulfides may increase, along with a rise in CS_2-related health effects.

This study specifically examines the toxicological mechanisms by which CS_2 can interfere with glucose metabolism and subsequent complications related to interference with normal glucose metabolism, including diabetes. Diabetes is a major risk factor for developing cardiovascular disease and costs the health-care system ~$174 billion a year. A study by Narayan et al predicted that the lifetime risk of developing diabetes (based on 2,000 figures) was 1:3 for male children, 2:5 for females, and 1:2 for Hispanic females.[13]

The purpose of this study is to raise awareness in the medical community, public health arena and regulators of the potential for glucose metabolic interference from CS_2 exposure, and the contribution of CS_2 to the atmosphere and air quality from UOG exploration and processing emissions.

Methods and Materials

A literature review was performed, and relevant articles were identified by a systematic search of Medline, TOXLINE, Scopus, and PubMed databases. Due to lack of recent literature, all study designs were included and there was no limitation to publication date. Keywords used in the search included: CS_2 and occupational exposures, CS_2 and oil and gas emissions, diabetogenic effect/diabetes, tryptophan (Trp) metabolism/CS_2 and Trp metabolism and vitamin B_6, and retinopathy disease/occupational exposures. Of the 1,007 articles retrieved, the authors excluded 950 articles. Exclusion criteria were health effects not related to glucose metabolism, CS_2 production, or laboratory tests with CS_2. Articles included (57) were retrieved as full texts and reviewed for specificity to the study topic.

Mechanism of Action

Uptake and metabolism of CS_2 by the body may be expressed physiologically in various ways, including disruption of normal metabolism, immune response, serotonin levels, and melatonin production. Chronic exposure may lead to diabetes and subsequent complications related to diabetes (renal disease, amputations, and retinopathy). Cardiovascular disease, cancer, immunodeficiency disorders, and neuropsychiatric conditions have also been reported with CS_2 exposure.[14] The CS_2 mechanism of action in disrupting normal glucose function is through interference in vitamin B_6 equilibrium by inhibiting the action of important catalytic enzymes required for Trp metabolism.

Trp is degraded through several pathways, including the kynurenine (Kyn; Trp–nicotinic acid pathway), serotonin pathway, bacterial degradation, and protein synthesis (Fig. 1). The Kyn pathway was the predominant pathway for Trp metabolism.[15,16]

Trp is initially oxidized in the liver by the enzyme tryptophan 2,3-dioxygenase (TDO), forming N-formylkynurenine (a formulated derivative of Kyn). In nonhepatic tissues, indoleamine 2,3-dioxygenase (IDO) initiates Trp oxidation. TDO and IDO are catalysts for the rate-limiting step in Trp degradation along the Kyn pathway, and therefore the ratio of TDO and IDO is a critical factor in Trp degradation and regulation.[17] Breakdown products of Trp include kynuramines, kynurenic acid (KYA), quinolinic acid, and picolinic acid, which ultimately produces nicotinamide adenine dinucleotide (NAD), the coenzyme responsible for cellular respiration in cells and integral to the Krebs' citric acid cycle and electron transport side chain (see Fig. 2).[15]

Vitamin B_6 plays a major role in converting Trp to niacin (vitamin B_3) with assistance from the vitamin B_6 coenzyme pyridoxal 5′-phosphate (P5P). Niacin regulates blood pressure and is a key nutrient in cardiovascular health. It helps the body break down proteins, fats, and carbohydrates. Niacin deficiency can impair energy production, resulting in fatigue and lethargy. Niacin also plays a key role in cellular communication and in growth and maturation of cells.

Clinical Consequences of Trp Metabolism Disruption

According to a study by Vasak and Kopecky, CS_2 has the ability to disrupt the equilibrium between different forms of vitamin B_6 interfering with the ability of pyridoxal, pyridoxine, and pyridoxamine, the three main forms of vitamin B_6, to interconvert and support the availability of P5P in niacin production (see Fig. 3).[18]

P5P, the active form of vitamin B_6, is a cofactor in over 100 different metabolic reactions, including glucose, lipid, amino acid, and Trp metabolism. A deficiency in P5P causes Trp breakdown to divert from the normal Kyn pathway to other less efficient pathways, resulting in a higher production of xanthurenic acid (XA). XA can cause an interference with insulin activity and impede energy production (see Fig. 2).

Kyn pathway and its breakdown products KYA and 3-hydroxykynurenine (3-HK) are integral to numerous biological functions, including immune system and inflammatory response.[19] 3-HK is the determinant step where P5P directs

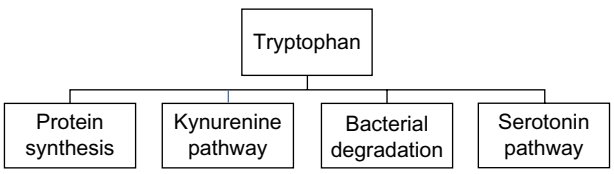

Figure 1. Pathways of Trp metabolism.

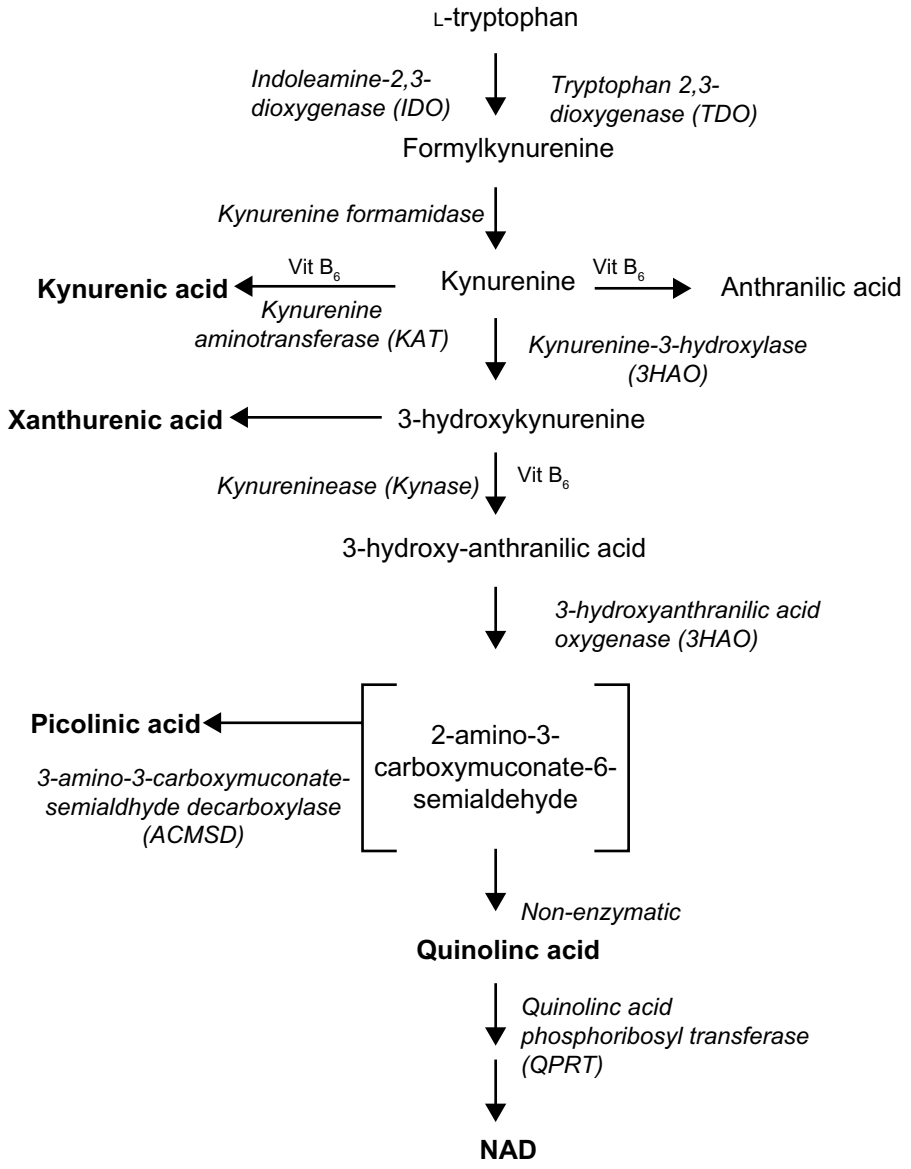

Figure 2. Production of NAD from Trp metabolism.

the production of NAD or the alternative XA in the Trp metabolic pathway.[17] Research by Munn and Mellor supports the theory that depletion of Trp by IDO allows tumor cells to escape immune system recognition.[20] IDO has also been found to affect the proliferation of T lymphocytes (T cells).[21] T cells play a key role in cell-mediated immunity.

Low serum Trp levels have been associated with numerous cancers, including colorectal, pancreatic, prostate, cervical, gastric, and ovarian.[22–24] Low serum Trp concentrations have also been identified as a key marker for inflammation and have been reported in patients with advanced stage lung cancer,[25] rheumatoid arthritis,[23] and immunocompromised patients.[26] A study by Wirleitner et al showed that patients with coronary heart disease had a significantly lower level of Trp in blood. Their study supported the theory that the immune-activated response of the body increased the rate of Trp metabolism leading to depleted Trp levels.[27]

Neuropsychiatric disorders have also been associated with low serum Trp. This is consistent with the fact that Trp production pathway produces serotonin and melatonin, key chemical compounds for the nervous system. Interference in the

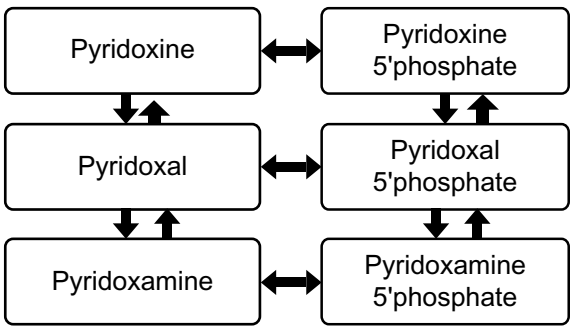

Figure 3. Interconversion of vitamin B_6.

Trp pathway results in a decreased production of serotonin and melatonin. Serotonin plays a key role in memory, learning, and behavior,[28,29] while melatonin regulates sleep cycle.[30] Changes in quinolinic acid, a by-product of the Kyn pathway, have been correlated with the presence of AIDS-related dementia.[26]

High levels of XA are a key indicator of Trp degradation through an alternate less efficient pathway. XA can damage insulin-producing beta cells in the pancreas and may lead to a diabetic state by interfering with insulin production and availability.[31–33] A study by Connick showed that an increase in XA levels resulted in decreased levels of active insulin.[31] The reduction in biological activity of the insulin–XA complex is explained by the fact that one molecule of XA is able to bind to one molecule of insulin monomer, resulting in a reduced biological activity of the XA–insulin complex (by ~49%) when compared to an insulin monomer alone.[34,35] Interference with glucose metabolism can indirectly cause other complications related to blood glucose disruption, including renal disease, amputations, and retinopathy, which may be preventable with early diagnosis and proper precautions. A study by Goto et al showed that CS_2 exposure produces a diabetogenic effect and pathogenesis of retinal microaneurysm similar to that in patients with diabetes mellitus.[36] Elevated levels of Kyn were also reported in the urine of patients with diabetic retinopathy. A study by Sugimoto et al showed that subjects with higher mean blood glucose levels suffer from retinopathy after exposure to CS_2.[37] Both the one-hour and two-hour postexposure blood glucose levels during prednisolone Glucose Tolerance Test were found to be higher in CS_2 workers than controls. Blood glucose levels were found to increase with the duration of CS_2 exposure.[38] A study by Bennink and Schreurs determined that blood glucose levels may be successfully improved in patients after treating them with vitamin B_6 supplements.[39] The mechanism by which CS_2 increases the potential of diabetic retinopathy is directly related to its role in the deficiency of vitamin B_6, specifically P5P, the active form of vitamin B_6 that acts as a required cofactor in the rate-limiting step in the Trp–Kyn and Kyn–NAD+ metabolic pathways, which ultimately results in insulin resistance (IR) by various metabolites.[17]

A study by Oxenkrug postulated that Kyn blocks N-methyl-D-aspartate receptors and the resulting antagonism indirectly causes an increase in glucose production. All of these compounds, XA, KYNA, QA, and 8-HQ, were found to inhibit proinsulin synthesis in isolated rat pancreatic islets.[17] The mechanism of Trp metabolism interference by CS_2 has been supported in animal studies. Allegri et al found Trp to be mainly metabolized along the Kyn pathway and increased levels of XA were excreted by vitamin B_6-deficient rats after ingestion of Trp, confirming the ability of CS_2 to interfere with normal Trp metabolic pathway.[40] Bender et al found excretion of XA to increase in vitamin B_6-deficient animals, while excretion of 4-pyridoxic acid decreased.[41] Exposure to CS_2 also resulted in vitamin B_6 deficiency in rats.[42] Animal studies also found similar adverse health effects associated with abnormal Trp metabolism related to a vitamin B_6 deficiency. Animal studies confirmed elevated excretion of XA in animals with a known pyridoxine (vitamin B_6) deficiency after ingestion of Trp.[31–33,43] This further supports the premise that increasing urinary XA levels are a valuable indicator of vitamin B_6 deficiency and disruption of the Trp pathway.

Excessive consumption of alcohol may also be a factor in disruption of the equilibrium in different forms of vitamin B. In mice, disturbance in pyridoxal metabolism has been seen with chronic intoxication.[44] Therefore, the synergistic effect of high intake of alcohol and occupational exposure to CS_2 may increase the potential for pyridoxal deficiency, contributing to glucose metabolism interference.[45]

The Cost of Diabetes

Research by the American Diabetes Association estimated the total cost of diagnosed diabetes in 2007 to be >$174 billion. Extrapolating this cost factor into 2012 figures shows the total cost to be in excess of $245 billion, representing a 71% increase in health-care costs when compared to 2007 costs. The 2012 direct cost estimates included $176 billion in medical costs and $69 billion in reduced productivity. Indirect costs (2012) included increased absenteeism ($5 billion), reduced productivity while at work of the employed population ($20.8 billion), reduced productivity for those not in the labor force ($2.7 billion), inability to work as a result of disease-related disability ($21.6 billion), and lost productive capacity due to early mortality ($18.5 billion).[46]

Individuals with diagnosed diabetes incur average medical expenditures of $13,700 per year, of which $7,900 is attributed to diabetes with medical expenditures ~2.3 times higher than what expenditures would be in the absence of diabetes. Maintaining blood glucose levels within normal range has been shown to prevent the onset of diabetic retinopathy.[46] Diabetic retinopathy is the most common cause of blindness in working-age American adults.[47]

Discussion

Environmental pollutants have the ability to interfere with normal cellular functions and can affect, on a molecular level, key metabolic pathways. The capacity of CS_2 to interfere specifically with vitamin B_6 production can initiate a cascade of critical vitamin deficiencies and dysregulate normal glucose metabolism, ultimately resulting in IR. Vitamins A, D, E, and K are fat soluble and could be stored in the fat and liver tissues for up to six months or until the body requires them. Water-soluble vitamins B complex and C are not capable of being stored in the body and must be replenished on a daily basis. Vitamin B complexes are critical to many reactions in the body, including assisting coenzymes in energy production from fat, carbohydrates, and protein metabolism and production of neurocompounds. Through the Trp production pathway, serotonin and melatonin are produced. Serotonin plays an important role in sleep, memory, learning, and behavior.[27,28]

CS_2 and associated sulfide compounds were found in elevated concentrations when compared to average background levels in this study in areas where UOG extraction and processing activities occurred. Therefore, residential communities where UOG exploration and processing operations occur may be exposed to elevated atmospheric levels of CS_2 and may be at an increased risk for glucose metabolism interference.

The effect of decreased levels of vitamin B_6 on sensitive populations, including children, pregnant women, the elderly, and immunocompromised, must be considered when permitting UOG extraction and processing in urban areas where sensitive populations reside. Children may experience greater effects from CS_2 exposure due to their unique physiological demands and immature immune system. According to the ATSDR, "Children exposed to same levels of CS_2 as adults may receive larger doses because they have relatively greater lung surface:body weight and higher minute volume:weight ratios. In addition, they may be exposed to higher levels than adults in the same location because of their short stature and the higher levels of carbon disulfide found nearer to the ground."[48] Additionally, CS_2 was found to be highly associated with other sulfide compounds. The effect of simultaneous multiple chemical exposures on a child is not well understood. The time of life exposure may also be a critical component on how physiologically detrimental the effect CS_2 may be. Pregnant women have a unique vulnerability to chemical exposures and may unintentionally expose their unborn child to toxic chemicals capable of crossing the placental barrier. Human epidemiological studies have shown the ability of chemicals to bioaccumulate in milk in occupationally exposed nursing mothers.[49,50] A study of 682 women occupationally exposed to CS_2 showed an increased rate of birth defects (1.3–2.5%) when compared to 745 women in the unexposed control group.[51] With exposure to elevated atmospheric levels of CS_2, the number of children diagnosed with diabetes may increase. Women on estrogen replacement therapy may potentially have a compounding deficiency, as estrogen replacement has been found to impact vitamin B absorption.[52] Current regulatory guidance on CS_2 exposure does not take into account the combined effect that simultaneous sulfide exposures can have, specifically on sensitive populations.

Limitations of this study include a lack of current information, recognition, and understanding of the ability of CS_2 to adversely affect health. CS_2 and other sulfide compounds have not been the focus of UOG emissions, and therefore, its contribution to atmospheric levels or impact to air quality is underrecognized. Medical professionals and public health regulators responsible for the protection of the public may benefit from this study, by providing more accurate diagnosis and protection to the public.

Conclusion

Atmospheric CS_2 was found to be present in elevated concentrations in residential areas where unconventional oil and gas operations were occurring when compared to UATMP national background atmospheric levels. CS_2 adversely affects multiple systems in the body and possesses the ability to dysregulate normal glucose metabolism, which can indirectly cause other complications (diabetes, neurodegenerative disease, and retinopathy).

Residential areas with UOG activities and UOG occupational workers are at a greater risk of health impairment due to the magnitude and frequency of CS_2 exposure. The recommendation of this research is for implementation of health screenings for glucose metabolic interference by physicians, school districts near UOG facilities, and UOG employers. Early detection and treatment may prevent the onset of abnormal glucose metabolism and reduce the cost of workers' compensation, medical treatment, and incurred costs from the complications of glucose metabolism interference.

Author Contributions

Conceived and designed the experiments: ALR, JTP, SSA. Analyzed the data: ALR, JTP, SSA. Wrote the first draft of the manuscript: ALR, JTP. Contributed to the writing of the manuscript: ALR, JTP, SSA. Agree with manuscript results and conclusions: ALR, JTP, SSA. Jointly developed the structure and arguments for the paper: ALR, JTP, SSA.Made critical revisions and approved the final version: ALR. All authors reviewed and approved of the final manuscript.

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