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April 24, 2006

To whom it may concern:

This letter is written on behalf of Mr. Robert Macfarlane a patient, whom I have evaluated for a diagnosis of myelodysplastic syndrome. I am a medical board certified oncologist currently in practice in Florida. My training in the field of oncology includes significant research and clinical experience in the diagnosis of hematologic malignancies.

Mr. Macfarlane is a 61-year old gentleman who was referred for hematologic evaluation following a several year history of macrocytic anemia. Ultimate work-up for this condition included a bone marrow examination which was performed on July 6, 2005, and led to a diagnosis of myelodysplastic syndrome (MDS) as the etiology of his macrocytic anemia. The key aspect of his bone marrow findings include a hypocellular marrow, dyserythropiesis, dysmegakaryopoiesis, and increased ringed sideroblasts. Because of the prolonged nature of his macrocytic anemia, it is presumed that Mr. Macfarlane's case of MDS evolved well before he reached 60 years of age.

Myelodysplastic syndrome is generally an idiopathic disease of the elderly and rarely occurs in patients under 60 years of age.^{1 2} In patients like Mr. Macfarlane who develop early onset MDS, their disease is usually due to prior exposure to mutagenic agents,³ either through treatment with chemotherapy or through

¹ <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.1994.tb06733.x/abstract>

by PJ Williamson - 1994 - Cited by 110 - Related articles

British Journal of Haematology. 1994. 87, 743-745. Establishing the incidence of myelodysplastic syndrome. P. J. WILLIAMSON, A. R. KRUGER, P. J. REYNOLDS, ...

² [French registry of acute leukemia and myelodysplastic syndromes ...](#)

[onlinelibrary.wiley.com](#) › ... › [Journal Home](#) › [Vol 60 Issue 6](#)

Jun 29, 2006 – Cancer. Volume 60, Issue 6, pages 1385–1394, 15 September 1987. Additional Information ... Cancer, 60: 1385–1394. doi: ...

³ [Intracellular IL-4, IL-10, and IFN-γ Levels of Leukemic Cells and ...](#)

www.annclinlabsci.org/cgi/reprint/36/1/7.pdf

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Lichtman MA, Liesveld JL. Acute myelogenous leukemia. In: Williams' Hematology, 6th ed (Beutler E., Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, Eds), ...

environmental/occupational exposure to genotoxins, particularly the aromatic hydrocarbons.⁴ Mr. Macfarlane has never received chemotherapy but from an occupational standpoint it is clear that Mr. Macfarlane was exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a known contaminant of herbicides while employed by the United States in Vietnam War. It is my medical opinion that Mr. Macfarlane's myelodysplastic syndrome is casually related to exposure to TCDD during his military service in Vietnam on the basis of both epidemiologic and mechanistic data.

From an epidemiologic standpoint, it is established that TCDD exposure is causally related to a variety of clonal bone marrow diseases. In fact, many of these malignancies are already presumed by the Veterans' Administration to be related to Agent Orange exposure and include all forms of non-Hodgkin's lymphomas, chronic lymphocytic leukemia, and multiple myeloma.⁵ An increased risk has been documented in agricultural workers⁶, an occupation in which exposure to dioxin-contaminated herbicides and pesticides is assumed.

Other studies have linked exposure to benzene to elevated risk for MDS.^{7 8} As will be described below, benzene and TCDD are known to exert their toxic effects via common molecular pathways. Further epidemiologic evidence derives from a 1976 industrial accident in Seveso, Italy, in which several thousand residents were exposed to TCDD. Studies of this population have revealed a probable relationship between TCDD exposure and an increased risk of acute myeloid leukemia.⁹ Because acute myeloid leukemia (AML) may arise from previously unrecognized antecedent MDS, this finding suggests the possibility that a portion of the increased risk of AML in the residents of Seveso may be due to TCDD-mediated MDS. In conclusion, available

⁴ [Myelodysplastic Syndrome: Etiology, Prognosis and Management ...](#)

[adisonline.com/.../Myelodysplastic_Syndrome__Etiology,_Prognosis_and...](#)

List AF, Doll DC. The myelodysplastic syndromes. In: Lee GR, Foerster J, Lukens J. Wintrobe's clinical hematology. 10th ed. Baltimore (MD): Lippincott ...

⁵ [Updated Vietnam Veterans & Agent Orange VHI 2005](#)

[www.vasvw.org/.../...](#)

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Deputy Director, Environmental Agents Service. VA Central Office or their survivors had to establish that the veteran served in Vietnam between ...

⁶ [Catherine Nisse - research profile on BiomedExperts](#)

[www.biomedexperts.com/Profile.bme/1024908/Catherine_Nisse - Cached](#)

Catherine Nisse - research profile on BiomedExperts:Environmental ... 2001: Nisse C; Haguenoer J M; Grandbastien B; Preudhomme C; Fontaine B; Brillet J M; Lejeune R; Fenaux P Occupational and environmental risk factors of the myelodysplastic ... living in northern France: lead burden levels and their determinants. ...

⁷ [Clinical Features of Hematopoietic Malignancies and Related ...](#)

[www.ncbi.nlm.nih.gov/pmc/articles/.../pdf/envhper00349-0224.pdf](#)

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MS. Hematopoietic malignancies and related disorders among benzene-exposed workers in China. *Leuk Lymph* 14:91-102. (1994). 23. Bennett JM, Catovsky D, ...

⁸ [Journal of Toxicology and Environmental Health, Part A BENZENE AND ...](#)

[superfund.berkeley.edu/pdf/318.pdf](#)

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Apr 27, 2010 – Hoover, R. N., and Linet, M. S. 1997. Benzene and the dose-related incidence of ... in China. *Environ. Health Perspect.* 104:1353–1364. ...

⁹ [Pesticides and Cancer](#)

[www.jstor.org/stable/3552701](#)

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Bertazzi A. Cancer in a young population in a dioxin-contaminated area. *Int J Epidemiol* 1993; 22: 1010-3. 121. Pesatori AC, Sontag JM, Lubin JH, ...

epidemiologic data support the possibility of a connection between TCDD exposure and the pathogenesis of MDS.

Beyond the epidemiologic findings, the identification and characterization of the aryl hydrocarbon receptor have provided substantial mechanistic evidence linking TCDD to the pathogenesis of malignant disease. In fact, this evidence was the basis for the 1997 decision of the International Agency for Research on Cancer (a division of the World Health Organization) to upgrade its categorization of TCDD from “possibly carcinogenic to humans” (category 2B) to “known to be carcinogenic to humans” (category 1).¹⁰ The aryl hydrocarbon receptor (AhR) is a highly conserved nuclear receptor and transcription factor stimulated by TCDD, which leads to the induction and suppression of numerous genes.^{11 12 13} Mutagenic/carcinogenic events occurring downstream of AhR stimulation include changes in cell signaling proteins,^{14 15 16 17} calcium mobilization, growth factors, oncogenes, and cell proteins. Members of aromatic hydrocarbon family known to activate AhR include benzene,¹⁸ benzene metabolites, and TCDD (an aromatic hydrocarbon containing two benzene rings). Recent

¹⁰ [IARC Working Group on the Evaluation of Carcinogenic Risks to ...](#)

www.ncbi.nlm.nih.gov/pubmed/9379504

1. IARC Monogr Eval Carcinog Risks Hum. 1997;69:1-631. ... Risks to Humans: Polychlorinated Dibenzo-Para-Dioxins and Polychlorinated Dibenzofurans. ...

¹¹ [Induction of cytochrome P4501A1.](#)

www.ncbi.nlm.nih.gov/pubmed/10331078

by JP Whitlock Jr - 1999 - [Cited by 681](#) - [Related articles](#)

1. Annu Rev Pharmacol Toxicol. 1999;39:103-25. ... Cytochrome P4501A1 is a substrate-inducible microsomal enzyme that oxygenates polycyclic aromatic ...

¹² [Cancer immunoediting and dioxin-activating aryl hydrocarbon ...](#)

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Dioxin revisited: developments since the 1997 IARC classification of dioxin as a human carcinogen. Environ Health Perspect 2004;112:1265-8. [PubMed] ...

¹³ [Dioxins and the ah receptor - Silbergeld - 2007 - American Journal ...](#)

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Jan 19, 2007 – Silbergeld, E. K. and Gasiewicz, T. A. (1989), Dioxins and the ah receptor. American Journal of Industrial Medicine, 16: 455–474. doi: ...

¹⁴ [Biological and chemical studies on the aryl hydrocarbon receptor ...](#)

www.sciencedirect.com/science/article/pii/S0024320511001056

by ML Fernández-Cruz - 2011

Feb 26, 2011 – AC CE PT ED M AN US CR IPT ACCEPTED MANUSCRIPT 25 Carlson DB, Perdew GH. A dynamic role of the Ah receptor in cell signalling? ... J Biochem Mol Toxic 2002;16:317- 25. Casado S, Alonso M, Herradon B, Navas JM. ...

¹⁵ [by Ivy D. Moffat A thesis submitted in conformity with the ...](#)

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by ID Moffat - 2008 - [Related articles](#)

Matsumura F (2003) On the significance of the role of cellular stress response reactions in the toxic actions of dioxin. Biochem Pharmacol 66:527-40. ...

¹⁶ [Interruption of estradiol signal transduction by 2,3,7,8 ...](#)

www.growth-factors.net/showabstract.php?pmid=9605431 - [Cached](#)

Biochem Pharmacol (1998) 55: 1077-90. Interruption of estradiol signal transduction by 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) ...

¹⁷ [Exposure to the dioxin 2,3,7,8tetrachlorodibenzopdioxin \(TCDD ...](#)

onlinelibrary.wiley.com/doi/10.1111/j.1600-0684.2001.tb00004.x/pdf

endocervical cells from macaques exposed to TCDD. Tox- icol Appl Pharmacol 151:283-293, 1998. 6. FERENCZY A, WINKLER B: Anatomy and histology of the cervix. ...

¹⁸ [Mechanism of Benzene-Induced Hematotoxicity and Leukemogenicity ...](#)

in vivo research molecular epidemiology research involving the victims of the Seveso accident has confirmed that TCDD exposure leads to predictable and consistent changes in the AhR pathway.^{19 20}

This growing body of mechanistic data regarding the aryl hydrocarbon receptor supports the presumption that aryl hydrocarbons, which include benzene and TCDD, act via a final common pathway in exerting their mutagenic effects. Because epidemiological studies correlate benzene exposure and the development of MDS (see foot notes 7-8),²¹ it is therefore plausible that TCDD exposure should carry identical risks. In the assessment of Mr. Macfarlane's case of MDS, it is important to note that it was very early onset, which previously described suggests its relationship to toxic exposures. It is also important to note that with the exception of to TCDD during his military service in the Vietnam War, Mr. Macfarlane has not been known to exposed to any other mutagenic toxins which may lead to MDS, including no know exposure to benzene, chemotherapy or radiation, or even cigarette smoking. Accordingly, it is my firm medical opinion that when Mr. Macfarlane's medical condition and history are viewed in totality, it is unlikely that anything other than TCDD exposure during his service in Vietnam caused his case of myelodysplastic syndrome.

Sincerely,

Timothy Aliff, M.D.

tpx.sagepub.com/content/32/2_suppl/12.refs

Aryl hydrocarbon receptor mediates benzene-induced hematotoxicity. *Toxicol Sci* 70, 150—6. Abstract/FREE Full Text. Yoon, B.I.; Li, G.X.; Kitada, K., ...

¹⁹ [Dioxin revisited: developments since the 1997 IARC classification ...](#)

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by Kyle Steenland, Pier Bertazzi, Andrea Baccarelli, Manolis Kogevinas. Comments ... TCDD-mediated alterations in the AhR-dependent pathway in Seveso, ... *Carcinogenesis* 24:673-680. Landi M, Needham L, Lucier G, Mocarelli P, Bertazzi P, ...

²⁰ [AS you know the symposium on dioxin exposures health effects on ...](#)

www.massey.ac.nz/~wwwcphr.../Dioxin%20Symposium%20proceedings.p...

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TCDD, which is the most toxic form of dioxin, is undoubtedly one of the most toxic chemicals made by humans. TCDD toxic effects are mediated by the aryl 149: 287-93. Baccarelli A, Pesatori AC, Consonni D, et al., (2005). ...

²¹ [Toxicological Review of Benzene: Cancer Aspect](#)

thailand.digitaljournals.org/index.php/TCJ/article/download/3043/2618

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by S Sangrajang - 2010 - [Related articles](#)

In this review, we summarize the impact on human health of benzene exposure, Yin SN, Li GL, Tain FD, Fu ZI, Jin C, Chen YJ, et al. ... workers exposed to benzene in China: overall results. *Am J Ind Med* 1996;29 :227-35. ...