Skin diseases associated with Agent Orange and other organochlorine exposures

Andrew T. Patterson, MD,[a,b] Benjamin H. Kaffenberger, MD,[a] Richard A. Keller, MD,[c] and Dirk M. Elston, MD[d,e]
Columbus, Ohio, and San Antonio, Texas

Organochlorine exposure is an important cause of cutaneous and systemic toxicity. Exposure has been associated with industrial accidents, intentional poisoning, and the use of defoliants, such as Agent Orange in the Vietnam War. Although long-term health effects are systematically reviewed by the Institute of Medicine, skin diseases are not comprehensively assessed. This represents an important practice gap as patients can present with cutaneous findings. This article provides a systematic review of the cutaneous manifestations of known mass organochlorine exposures in military and industrial settings with the goal of providing clinically useful recommendations for dermatologists seeing patients inquiring about organochlorine effects. Patients with a new diagnosis of chloracne, porphyria cutanea tarda, cutaneous lymphomas (non-Hodgkin lymphoma), and soft-tissue sarcomas including dermatofibrosarcoma protuberans and leiomyosarcomas should be screened for a history of Vietnam service or industrial exposure. Inconclusive evidence exists for an increased risk of other skin diseases in Vietnam veterans exposed to Agent Orange including benign fatty tumors, melanomas, nonmelanoma skin cancers, milia, eczema, dyschromias, disturbance of skin sensation, and rashes not otherwise specified. Affected veterans should be informed of the uncertain data in those cases. Referral to Department of Veterans Affairs for disability assessment is indicated for conditions with established associations. (J Am Acad Dermatol 2016;74:143-70.)

Key words: Agent Orange; chloracne; dioxin exposure; organochlorine; skin disease; veteran; Vietnam; 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Dermatologic ailments were the most common reason for outpatient visits to US Army medical facilities during the Vietnam War and the major cause of field days lost.[1] Although immersion foot and zoonotic tinea comprised much of the acute dermatologic morbidity, long-term effects can often relate to organochlorine exposure. During the war, herbicides were used to defoliate enemy crops and cover in a campaign designated Operation Ranch Hand (ORH), lasting from 1962 to 1971. It exposed millions of soldiers and civilians to organochlorine chemicals, predominantly Agent Orange containing 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).[2] Resultant skin diseases have been

Abbreviations used:

AFHS:	Air Force Health Study
CDC:	Centers for Disease Control and Prevention
NMSC:	nonmelanoma skin cancer
ORH:	Operation Ranch Hand
PCT:	porphyria cutanea tarda
TCDD:	2,3,7,8-tetrachlorodibenzo-p-dioxin
VA:	Department of Veterans Affairs

From the Division of Dermatology, Ohio State University College of Medicine[a]; US Air Force, San Antonio Military Medical Center[b]; Dermatology, Audie L. Murphy Veterans Hospital, San Antonio, US Air Force[c]; Ackerman Academy of Dermatopathology[d]; and US Army (Retired).[e]

Funding sources: None.

Disclosure: Dr Keller is a full-time employee of the US Department of Veterans Affairs. Dr Patterson is employed as an active duty member of the US Air Force. Drs Kaffenberger and Elston have no conflicts of interest to declare.

The contents of this article represent the authors' views and opinions, but do not represent the views or policy of the US Department of Veterans Affairs or the US Armed Forces.

Accepted for publication May 5, 2015.

Reprint requests: Benjamin H. Kaffenberger, MD, Ohio State University Dermatology, 915 Olentangy River Road, Suite 4000, Columbus, OH 43212. E-mail: Benjamin.Kaffenberger@osumc.edu.

Published online July 23, 2015.

0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.05.006

a persistent question with one study reporting up to 85% of exposed veterans describing a persistent skin eruption.[3,4] An official review has been conducted by the Institute of Medicine with specific emphasis on systemic manifestations including cancers, fertility, and cardiovascular, metabolic, neurologic, and immunologic parameters of Agent Orange exposure, but with little emphasis on skin disease.[5] This article provides a brief description of organochlorine use, disease mechanism, and a summary of evidence for dermatologic conditions associated with organochlorine exposure.

CAPSULE SUMMARY

- Organochlorines are highly toxic chemicals with long half-lives.
- Human exposure has occurred through industrial accidents and defoliation missions during the Vietnam War.
- This systematic review summarizes the dermatologic evidence of exposure associations and offers clinical guidelines for dermatologists.

METHODOLOGY

Journal articles were searched and selected on a narrative basis to provide an overview of organochlorine history and pathophysiology. Skin disease associations were assessed systematically by 2 investigators (A. T. P., B. H. K.) using search terms "Agent Orange," "dioxin," "2,3,7,8-tetrachlorodibenzo-p-dioxin," OR "TCDD" AND "skin," "cutaneous," "rash," "skin cancer," "dermatol*," "chloracne," "acne," OR "porphyria cutanea tarda" (PCT). Abstracts were reviewed by both investigators and selected for studies on 1 or more human beings. References were cross-checked for additional inclusion (Fig 1). A third investigator (D. M. E.) made final inclusion decisions for disagreements.

HISTORICAL EXPOSURE

Although numerous phenoxyherbicide formulations were used as defoliants in Vietnam and the Korean demilitarized zone, the most prominent involved a 1:1 mixture of *n*-butyl esters 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. This particular mixture became known as Agent Orange, as herbicides were identified by colored stripes on the sides of the 55-gal transport barrels.[6,7] Agent Orange is now accepted as reference to all military phenoxyherbicides used during the era. The synthesis of the 2,4,5-trichlorophenoxyacetic acid component from 2,4,5-trichlorphenol generated the highly toxic byproduct TCDD, which remained in the mixture. Dioxins are a group of lipophilic, biologically active, chlorinated aromatic compounds produced during industrial manufacturing reactions that possess long-lasting environmental pollutant capacity.[6,8] TCDD contamination levels varied between 1 and 50 ppm in individual barrels with an estimated average mean concentration of 13 ppm.[2,7] Although Vietnam serves as the largest organochlorine exposure historically, contact risks may still persist in occupational settings including paper mills, pesticide manufacturing, incineration/combustion, and metallurgy.[7] Another prominent large-scale dioxin exposure occurred in 1976 in Seveso, Italy, when a chemical manufacturing plant released several tons of organochlorine-laced chemicals into the surrounding towns. Thousands of residential citizens were exposed to high levels of TCDD and numerous longitudinal studies were conducted examining the effects of dioxins on human beings.[5,7] Another highly publicized case of TCDD toxicity involved the 2004 assassination attempt on Ukrainian presidential candidate Viktor Yushchenko, where high dioxin levels led to substantial chloracne development (Fig 2).[9-11] This article attempts to examine all organochlorine human exposures described in the literature for any available information on cutaneous toxicity in human beings.

AGENT ORANGE

Throughout the course of ORH, almost 20 million gal of Agent Orange—containing an estimated 366 kg of TCDD—was applied to over 3.6 million acres across south Vietnam.[7] The goal was to decimate vegetation used for enemy food and concealment while clearing land near allied bases for easier defense.[6] Despite increased effort to characterize the degree and distribution of dioxin based on military records, quantifying the extent of individual exposure to Agent Orange has proved challenging for researchers.[2] The expensive serum dioxin test, considered to be the gold standard for organochlorine exposure, has only been used by a few high-level evidence studies to date because of its high cost and lack of resultant impact on clinical management. The Department of Veterans Affairs (VA) does not perform this test as by law the VA presumes all US service branch members who served in Vietnam or Korea during certain specified time periods were exposed to Agent Orange, along