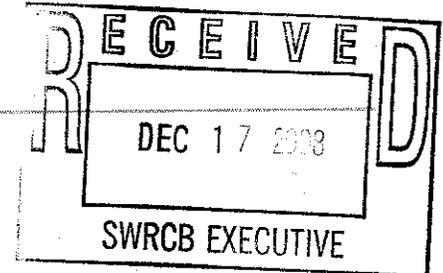


commentletters - Comments on Proposed Recycled water policy

From: Edo McGowan <edo_mcgowan@hotmail.com>
To: <commentletters@waterboards.ca.gov>, <owl@owlfoundation.net>, <meyer@sbcc.edu>
Date: Wednesday, December 17, 2008 11:53 AM
Subject: Comments on Proposed Recycled water policy



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Members---State Water Resources Control

Re: Comments on Proposed Recycled Water Policy and Draft Staff Report---Endocrine Disrupters within Recycled water

Fm: Dr Edo McGowan

A few days ago, I sent your Board a note on the proposed water recycling policy indicating that endocrine disrupting materials could be found in the currently produced recycled water. To augment that note, I am presenting the following.

Alkylphenol Ethoxylate Degradation Products (AEDPs) and other endocrine disrupter compounds (EDCs) as found in sewage and its byproducts, including recycled water were shown in my previous submittal to have the potential to build up in soils, within plants that are consumed by humans as well as consumed by food animals, hence via the food chain, can adversely impact humans. Because EDCs are able to impact the immune system at very low levels, the issue needs to be explored in greater detail by your board and again points to the fact that conclusions within the Draft Staff Report may be in serious error. That also may mean that the make up of the Blue-Ribbon Panel (BRP) will need adjustment to reflect sufficient expertise to evaluate these potential adverse impacts. Thus the Board will need to consult with the academic environment for suggestions on what kind of persons would be best able to interact with the BRP and thus give guidance to the Board.

Regulatory T cells (sometimes known as suppressor T cells) are a specialized subpopulation of T cells that act to suppress activation of the immune system and thereby maintain immune system homeostasis and tolerance to self-antigens. When these regulatory T cells are adversely impacted, one sees the development of autoimmune diseases.

In catching up on my reading I noted in the October 10 edition of SCIENCE a paper by Shevach (p. 202), actually a short article, on immunology and specifically regulatory T cells. The role of cytotoxic T lymphocyte 4 antigen (CTLA-4) restrains the immune system thus reduce autoimmune responses. The question that came to mind, what are the effects of EDCs, as found in sewage and recycled water on CTLA-4? Evidently some of the EDCs do have the capacity to affect CTLA-4 and other T cell receptors.

In addition, T helper cells are affected by EDCs and these play a critical role in establishing and maximizing the capabilities of the immune system.

In these cases, it is important to remember the **precautionary principle**. The precautionary principle is both a moral and political obligation which falls with great weight upon decision makers. It states that **if** an action or policy might cause severe or irreversible harm to the public or to the environment, in the absence of a scientific consensus that harm **would not** ensue, the burden of proof falls on those who would advocate taking the action. The principle implies that there is a

responsibility to intervene and protect the public from exposure to harm where scientific investigation notes a plausible risk.

Exposure to 4-*tert*-octylphenol, an environmentally persistent alkylphenol, enhances interleukin-4 production in T cells via NF-AT activation

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Available online 27 March 2004.

Abstract

4-*tert*-Octylphenol (OP) is a representative endocrine disruptor that may have adverse effects on human health. The influence of this compound on allergic immune responses remains unclear. In this study, we have examined the effects of OP on production of interleukin-4 (IL-4), a pro-inflammatory cytokine closely associated with allergic immune responses. OP significantly enhanced IL-4 production in antigen-primed T cells in a dose-dependent manner. Treatment with OP in vivo resulted in significant increase of IL-4 production in T cells and of IgE levels in sera of antigen-primed mice. Furthermore, OP enhanced the activation of IL-4 gene promoter in EL4 T cells transiently transfected with IL-4 promoter/reporter constructs, and the enhancing effect mapped to a region in the IL-4 promoter containing binding sites for nuclear factor of activated T cell (NF-AT). Activation of T cells by phorbol-12-myristate-13-acetate (PMA) resulted in markedly enhanced binding activities to the NF-AT site, which significantly increased upon addition of OP, indicating that the transcription factor NF-AT was involved in the enhancing effect of OP on IL-4 production. The enhancement of IL-4 production by OP was blocked by FK506, a calcineurin inhibitor, but not by the estrogen receptor (ER) antagonist ICI 182 780. FK506 inhibited the NF-AT-DNA binding activity and IL-4 gene promoter activity enhanced by OP in a dose-dependent manner. These findings demonstrate that OP enhances IL-4 production in T cells via the stimulation of calcineurin-dependent NF-AT activation.

Effects of Various Chemicals Including Endocrine Disruptors and Analogs on the Secretion of Th1 and Th2 Cytokines from Anti CD3-Stimulated Mouse Spleen Cells

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The *in vitro* effects of various chemicals, such as styrene dimers,

styrene trimers, alkylphenols, phthalate esters, phytoestrogens, and organotin compounds, on the production of interferon-gamma (IFN- γ), a type 1 helper T-cells (Th1) specific cytokine, and interleukin-4 (IL-4), a type 2 helper T-cells (Th2) specific cytokine, which are secreted from anti CD3-stimulated mouse spleen cells, were examined. These chemicals suspected of having an endocrine disruptor function and to which humans may become exposed *via* ingestion through food, food containers, and food packaging. It was found the organotin compounds bis(tributyltin) oxide, tributyltin chloride, and dibutyltin dichloride at concentrations which did not elicit any cytotoxicity inhibited secretion of the Th1 and Th2 specific cytokines IFN- γ and IL-4 at concentrations (0.01-0.03, 0.07-0.1, and 0.096-0.132 μ M for IC₅₀, respectively) that were much lower than those of the other chemicals. However, these butyltin compounds exhibited similar degrees of inhibitory effects on IFN- γ and IL-4 secretion and did not selectively inhibit the secretion of one or the other cytokine. However, diphenyltin dichloride and phenyltin trichloride enhanced the secretion of IL-4 at the comparatively low concentrations of 0.3 μ M and 1.0 μ M, respectively, although these compounds significantly inhibited IFN- γ secretion at the same concentrations. In addition, 4-*t*-pentylphenol enhanced IL-4 secretion although it inhibited IFN- γ secretion at the comparatively high concentration of 30 μ M. It was also found that some styrene trimers, phthalate esters and flavonoids as well as the alkyl phenols octylphenols and nonylphenol among others, inhibited the secretion of both cytokines at comparatively high concentrations (< 30 μ M).

Key words spleen cells, type 1 helper T-cells, type 2 helper T-cells, cytokines, endocrine disruptors

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The endocrine disruptors nonylphenol and octylphenol exert direct effects on T cells to suppress Th1 development and enhance Th2 development

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Abstract

Some endocrine disrupting chemicals (EDCs) have been evidenced to affect cytokine production and lymphocyte proliferation. However, it is unknown whether EDCs disturb Th1/Th2 development. We chose alkylphenols that have been widely used as plastic additives and surfactants, and some of them are recognized as xenoestrogens. We examined whether they exert direct effects on T cells to suppress or enhance Th1/Th2 development. We used two experimental systems with isolated T cells *in vitro*. In one system, isolated CD4⁺CD8⁺ thymocytes differentiated into Th1 and Th2 by two transient stimulations and cytokine treatment. In the second system, purified naïve CD4⁺ T cells from DO11.10 T cell receptor-transgenic and RAG-2-deficient mice differentiate into Th1 and Th2 by the treatment with cytokines and antibodies to CD3 and CD28. In both systems, 1–10 μ M of *p*-

n-nonylphenol suppressed Th1 development and enhanced Th2 development, whereas estrogen by itself failed to affect Th1/Th2 development. *p*-*n*-Octylphenol elicited similar effects, but 4-nonylphenol and *p*-*t*-octylphenol elicited much weaker effects. *p*-*n*-Dodecylphenol or *p*-*n*-octylbenzene failed to affect Th1/Th2 development. Thus, the length and branching of the alkyl side chain appeared to affect the activity. Although some alkylphenols have been suggested to have a weak affinity to retinoic acid receptors (RAR) or progesterone receptor (PRGR), antagonists of RAR, PRGR, glucocorticoid receptor (GCR), or retinoid X receptors (RXR) failed to inhibit the activity. These results suggest that *p*-*n*-nonylphenol and *p*-*n*-octylphenol directly suppress Th1 development and enhance Th2 development through mechanisms independent of estrogen receptors, RAR, RXR, PRGR, and GCR.

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Environmentally Induced Autoimmune Diseases: Potential Mechanisms

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- Tolerance
- Mechanisms Disrupting Tolerance
- Abnormalities of Tolerance Induction by Deletion
- Modification of Cellular Gene Expression
- Antigen Modification
- Conclusions

Abstract

Environmental and other xenobiotic agents can cause autoimmunity. Examples include drug-induced lupus, toxic oil syndrome, and contaminated l-tryptophan ingestion. Numerous mechanisms, based on *in vitro* evidence and animal models, have been proposed to explain how xenobiotics induce or accelerate autoimmunity. The majority of these can be divided into three general categories. The first is those inhibiting the processes involved in establishing tolerance by deletion. Inhibiting deletion can result in the release of newly generated autoreactive cells into the periphery. The second mechanism is the modification of gene expression in the cells participating in the immune response, permitting lymphocytes to respond to signals normally insufficient to initiate a response or allowing the antigen-presenting cells to abnormally stimulate a response. Abnormal gene expression can thus disrupt tolerance maintained by suppression or anergy, permitting activation of autoreactive cells. The third is the modification of self-molecules such that they are recognized by the immune system as foreign. Examples illustrating these concepts are presented, and related mechanisms that have the potential to similarly affect the immune system are noted. Some mechanisms appear to be common to a variety of agents, and different mechanisms appear to produce similar diseases. However, evidence that any of these mechanisms are actually responsible for xenobiotic-induced human autoimmune disease is still largely lacking, and the potential for numerous and as yet unidentified mechanisms also exists. *Key words: anergy, autoimmunity, deletion, mechanisms, suppression, tolerance, xenobiotic.*-- *Environ Health Perspect* 107(suppl 5) :737-742 (1999) .

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evidence for the Role of Environmental Agents in the Initiation or Progression of Autoimmune Conditions **Jonathan J. Powell, Judy Van de Water, and M. Eric Gershwin**

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- Mercury
- Iodine
- Vinyl Chloride
- Canavanine
- Ultraviolet Radiation and Ozone
- Organic Solvents
- Silica
- Particulates

- Anilides and L-Tryptophan

Abstract

The concordance of autoimmune disease among identical twins is virtually always less than 50% and often in the 25-40% range. This observation, as well as epidemic clustering of some autoimmune diseases following xenobiotic exposure, reinforces the thesis that autoimmune disease is secondary to both genetic and **environmental factors**. Because nonliving agents do not have genomes, disease characteristics involving nonliving xenobiotics are primarily secondary to host phenotype and function. In addition, because of individual genetic susceptibilities based not only on major histocompatibility complex differences but also on differences in toxin metabolism, lifestyles, and exposure rates, individuals will react differently to the same chemicals. With these comments in mind it is important to note that there have been associations of a number of xenobiotics with human autoimmune disease, including mercury, iodine, vinyl chloride, canavanine, organic solvents, silica, l-tryptophan, particulates, ultraviolet radiation, and ozone. In addition, there is discussion in the literature that raises the possibility that xenobiotics may also exacerbate an existing autoimmune disease. In this article we discuss these issues and, in particular, the evidence for the role of environmental agents in the initiation or progression of autoimmune conditions. With the worldwide deterioration of the environment, this is a particularly important subject for human health. *Key words:* autoimmunity, environmental agents, MHC, pollution, self-antigen, xenobiotic -- *Environ Health Perspect* 107(suppl 5) :667-672 (1999) .

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Autoimmune diseases associated with drugs, chemicals and environmental factors

David D'Cruz

Abstract

Autoimmune connective tissue diseases are complex multisystems and may be life threatening. Their aetiology is unknown but genetic, hormonal and environmental factors are important. In systemic lupus erythematosus (SLE), factors such as UV light and drugs, including oestrogen, may trigger the disease; silica exposure may also be important. Scleroderma is associated with silica exposure and drugs such as bleomycin and pentazocine may induce scleroderma-like diseases. Organic solvents such as vinyl chloride and epoxy resins may also be associated with scleroderma-like illnesses. The toxic oil syndrome and eosinophila-myalgia syndrome are best known examples of connective tissue diseases induced by chemical exposure. The systemic vasculitides and in particular cutaneous vasculitis may be induced by drugs and possibly environmental factors. A number of autoimmune connective tissue diseases may therefore be associated with exposure to drugs, chemicals and environmental factors and the risks associated with these should be minimised where possible.

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