

# Non-positive autoimmune responses against CYP2E1 in refrigeration mechanics exposed to halogenated hydrocarbons

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## Abstract

The aim of the study was to determine if occupational exposure to hydrofluorocarbons (HFC) and hydrochlorofluorocarbons (HCFC) generates autoimmune responses against CYP2E1. HFCs and HCFCs have replaced the chlorofluorocarbons (CFC) in e.g. refrigeration installations and air-conditioning systems. During the substitution period, refrigeration mechanics reported symptoms like asthma, influenza-like reactions, and joint troubles. These symptoms resemble those of chronic inflammatory diseases with an autoimmune component. Since exposure to structurally similar chemicals, e.g. halothane, has previously been associated with autoimmune responses and diseases, autoimmunity among the refrigeration mechanics might hypothetically explain the reported inflammatory symptoms.

Serum from 44 Swedish men, occupationally exposed to halogenated hydrocarbons, was screened for antibodies against CYP2E1 with enzyme-linked immunosorbent assay. Thirty of the workers had asthma, joint problems or influenza-like symptoms whereas 14 of them had no such symptoms. They were all selected from a cohort of 280 refrigeration mechanics. Unexposed, healthy, Swedish men ( $n=35$ ) constituted control group. The study was approved by the Ethics Committee at Karolinska Institutet.

No increase in autoantibodies against CYP2E1 was detected among the occupationally exposed workers as compared to the unexposed controls. Further, there was no difference in antibody titer between the exposed workers with symptoms and the exposed, asymptomatic workers or the unexposed controls. The present study does not completely exclude a connection between exposure and effect but makes the relation less likely at these exposure levels.

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## 1. Introduction

It is well known that people exposed to anesthetics like halothane, enflurane, isoflurane, desflurane, and similar substances may develop antibodies against proteins modified by their reactive metabolites as well

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as autoantibodies against cytochrome P450 2E1 (CYP2E1). CYP2E1 represents the main metabolic pathway of these compounds. In some cases the immune reactivity has resulted in liver damage, and rarely even in fatal injury (Bourdi et al., 1996; Martin et al., 2001; Njoku et al., 2002). Structurally similar halogenated hydrocarbons, i.e. hydrochlorofluorocarbons (HCFC) and hydrofluorocarbon (HFC), are commonly used in refrigeration installations like freezers and air-conditioning applications. Like halothane these substances are substrates of CYP2E1 (Dekant, 1996).

In 1998 some Swedish refrigeration mechanics were concerned about exposure to HCFCs and HFCs. These substances were used to replace the ozone depleting chlorofluorocarbons (CFC) in e.g. refrigeration applications. Some of the workers reported symptoms like headache and joint symptoms (Ahlborg et al., 1999; Hagberg and Lillienberg, 1999). A subsequent cross-sectional questionnaire study revealed an increased incidence of asthma, joint symptoms and influenza-like symptoms among persons occupationally exposed to refrigerants (Ahlborg et al., 1999). These symptoms resemble those of chronic inflammatory diseases with an autoimmune component. Consequently, workers who are occupationally exposed to these substances may hypothetically develop autoreactivity against CYP2E1. In addition, autoimmune responses have been reported in humans accidentally exposed to the refrigerants 1,1-dichloro-2,2,2-trifluoroethane (HCFC 123) and 1-chloro-1,2,2,2-tetrafluoroethane (HCFC 124) (Hoet et al., 1997). The refrigeration mechanics are moderately exposed to refrigerants at work. Nevertheless, peak exposures may occur, especially during evacuation of cooling systems and drainage and refilling of compressor oils (Gjølstad et al., 2003; Hagberg and Lillienberg, 1999). The substitution process caused additional exposure to new as well as old refrigerants among refrigeration mechanics. They were also exposed to compressor oils; mineral oils from the old CFC based systems and ester oils from the current HFC based systems (Hagberg and Lillienberg, 1999).

The autoimmune response is associated to reactive intermediates, i.e. halogenated acetyls and acetaldehydes, which are formed during metabolism. Thus, during metabolism of HFCs, HCFCs, and halothane, reactive halogenated acetyls and acetaldehydes are formed (Anders, 1991; Gandolfi et al., 1980). These may either react with water to form trifluoroacetic acid, or bind to a liver protein yielding a trifluoroacetyl protein. Since the formation of the reactive metabolites is mediated by CYP2E1, a large proportion of adducts are likely to be CYP2E1 adducts. These adducts may

subsequently induce an autoimmune response resulting in antibodies against trifluoroacetyl-CYP2E1. Formation of antibodies against native CYP2E1 may also be elicited due to a decreased tolerance, probably caused by the presence of the trifluoroacetyl-CYP2E1 neoantigen.

To test our hypothesis we collected serum samples from refrigeration mechanics who had been occupationally exposed to halogenated hydrocarbons, and measured their anti-CYP2E1 reactivity by enzyme-linked immunosorbent assay (ELISA). In addition, we have examined whether occupationally exposed persons with symptoms of potential autoimmune origin had increased anti-CYP2E1 autoreactivity compared to exposed but healthy persons. Since earlier or simultaneous exposure to halothane or other halogenated anesthetics may generate later autoimmune responses caused by other chemicals with the same metabolic pathway (e.g. HFC or HCFC), previous exposure to inhalation anesthetics was considered in the analyses. Age and cigarette smoking are other factors that could influence autoimmunity and hence were also considered.

## 2. Materials and methods

### 2.1. Subjects

Of the 79 volunteers that participated in the study, 44 were male workers presently or previously exposed to refrigerants at work. The remainders were 35 unexposed, healthy, male controls.

The exposed persons were selected from a nested case-control study of refrigeration mechanics belonging to the Swedish Building Workers' Union (Lillienberg et al., 2002). In that study, 280 subjects were telephone interviewed by a physician and an occupational hygienist about symptoms related to asthma, influenza-like symptoms, problems with joints, and occupational exposure conditions (Appendix A). In this study, the subjects with the most severe symptoms (Exposed with symptoms, Table 1) and the healthiest ones (Exposed without symptoms, Table 1), who were also living in Southern or Central Sweden, were selected.

A scoring system was developed in order to rank the severity of symptoms of individuals (Appendix B). To select the subjects encountering the most severe symptoms, the answers on certain questions in the study by Lillienberg et al. (2002) were given scores depending on the likeliness of an inflammatory disease. A maximum score of 20 were given for each of four symptoms (swollen or painful joints, asthma, influenza-like symptoms with fever and shivers, and rheumatoid

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