

Case Report

Occupational Obstructive Airway Diseases Caused by the Natural Gas Odorant Tetrahydrothiophene—Two Case Reports

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Background Tetrahydrothiophene (THT) is frequently used to odorize natural (city) gas. Only sparse data on adverse health effects of THT on humans are available.

Methods We performed a literature search and clinical investigations including case history and cardiopulmonary diagnostic tests in two symptomatic THT-exposed outpatients.

Results The two THT-exposed city workers developed transient neurologic symptoms such as nausea, vomiting, headaches, as well as skin and mucosa irritation, chronic rhinitis, chronic obstructive pulmonary disease, arterial hypertension, and cardiac arrhythmia. The neurological symptoms and respiratory disorders were found to be caused by intermittently high THT exposures. In favor of a causal relationship were severe work-related neurological and respiratory symptoms in previously healthy workers, results of animal experiments, and another report with very similar findings in the literature. The etiology of arterial hypertension and cardiac arrhythmia, however, remains unclear.

Conclusions Our two case reports demonstrate that repeated high THT-exposures can—in addition to neurotoxic symptoms—elicit chronic obstructive pulmonary disease. We recommend improved primary and secondary preventive measures, including the establishment of a TLV. Am. J. Ind. Med. 2009. © 2009 Wiley-Liss, Inc.

KEY WORDS: tetrahydrothiophene; irritant; COPD; arrhythmia

Abbreviations: CNS, central nervous system; COPD, chronic obstructive pulmonary disease; D_{LCO} , carbon monoxide diffusion capacity; ECG, electrocardiogram; FEF_{50} , forced expiratory flow at 50% of the vital capacity; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GPT, glutamic pyruvic transaminase; IG, intrathoracic gas volume, measured by bodyplethysmography; LC50, lethal concentration 50; MAK, Maximale Arbeitsplatz-Konzentration (maximum workplace concentration; Germany); NOAEC, no observed adverse effect concentration; P_{a,O_2} , arterial oxygen tension; R_{aw} , airway resistance, measured by body plethysmography; THP, tetrahydrothiophene; TLV, threshold limit value; TLC, total lung capacity.

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The authors confirm herewith that they have no conflict of interest.

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INTRODUCTION

Tetrahydrothiophene (THT; formula C₄H₈S; CAS 110-01-0; MW 88.17 g/mol; vapor pressure 2.4 kPa at 25°C; no TLV in the USA, MAK in Germany 50 ml/m³ [180 mg/m³; Deutsche Forschungsgemeinschaft, 2007]; R phrases 20/21/22-36/38¹ (Directive 67/548 EEC) [European Union, 2001, 2004] has for many years been used as natural gas odorant, solvent, insecticide, chemical intermediate, bird and moth repellent. It has a heterocyclic structure, is colorless, insoluble in water and chemically stable. Its odor is strong and unpleasant [Henschler, 1979; Krieger, 1994;

¹ Harmful by inhalation, in contact with skin and if swallowed, irritating to eyes and skin.

Greim, 2006, 2007; GESTIS Database, 2009; National Institute of Health, 2009; New Jersey Department of Health and Senior Services, 1999]. The olfactory threshold is 0.001 ml/m^3 air.

In vivo, THT is intermediately oxidized to THT-1,1 dioxide and 3 hypoxy-TNT-1,1 dioxide, methylated and excreted mainly via urine in the form of methyl-sulphonium derivatives.

The 4 hr inhalation LC50 of rats and the 2 hr LC50 of mice are $6,000\text{--}8,000 \text{ ml/m}^3$. Animal experiments to determine the acute toxicity following inhalation showed dysfunction of the central nervous system (hyperactivity, motor hyperreflexia, sedation, narcosis), irritation of eye and nose mucosa, dyspnea associated with hyperinflation and severe lung damage, peripheral vasodilation, and, when combined with adrenalin, cardiac arrhythmia, and bradycardia [Thuranszky et al., 1973; Pennwalt Corporation, 1975, 1985, 1986; Henschler, 1979; Syracuse Research Corporation, 1996; Greim, 2006, 2007; European Commission, European Chemicals Bureau, ed. IUCLID Dataset, 2000; National Institute of Health, 2009].

Chronic inhalation tests with mice and rats showed lacrimation, hypersalivation, liver dysfunctions and behavior disorders (hyperactivity, temporary aggression followed by depression) [Mikhaillets et al., 1964; Greim, 2006, 2007].

A study of the effect of THT on pregnant rats revealed an NOAEC of 234 ml/m^3 for maternal toxicity (nose, eye, and skin irritation, agitation) and of $1,910 \text{ ml/m}^3$ for adverse fetal effects [Pennwalt Corporation, 1988].

Oral uptake additionally induced damage to liver, kidneys, and intestines [Pennwalt Corporation, 1985].

Monkeys were found to be more sensitive to the primary THT metabolite tetrahydrothiophene-1-1 dioxide than dogs and dogs more sensitive than rodents [Andersen et al., 1977].

The effects of THT on human beings have been sparsely recorded [Deutsche Forschungsgemeinschaft, 2006, 2007; New Jersey Department of Health and Senior Services, 2009]. Inhalation is reported to lead to a general unease, vomiting, loss of appetite, gastric irritations, dysphagia, irritations of conjunctiva and airways, cough, dyspnea, and olfactory dysfunction. In addition, headaches, vertigo, nausea, palpitations, heat lability, and alcohol intolerance are evidence of systemic, cardiac, and central nervous system effects. Lymphopenia was also observed. Skin contact triggers local hyperemia and tingle [Krieger, 1994; Syracuse Research Corporation, 1996; GESTIS Database, 2009; New Jersey Department of Health and Senior Services, 2009].

CASE A

A 73-year-old male who had never smoked worked as a plumber, performing mainly residential repairs between 1947 and 1983. He worked for the city's department of works

during the last 18 years of his career. From 1968 to 1971, he was responsible for the THT odorization of natural gas. He performed this activity using a special box of $70 \text{ cm} \times 100 \text{ cm} \times 70 \text{ cm}$ in dimensions installed in a chamber without ventilation. Prior to depositing a 20 L tin bucket with liquid THT in the system, he had to pry off the lid of the bucket with tongs. This was performed without use of personal protective measures. From 1970 to 1971, he knocked a hole in the bucket using a pointed hammer. After pouring the liquid THT, he manually removed the old bucket that still contained THT residues. To exchange buckets, it was necessary to open and then close the cover of the special box secured by 42 screws using a screwdriver. He performed this procedure once to three times per week, each episode lasting an hour, and reported an extremely unpleasant odor. Due to splashing, mainly of the hands but also of other body parts, he came into contact with the substance. He reported that his clothes were frequently soaked. Exhaust ventilation was not available. The technical consulting service of the statutory accident insurance institution estimated that the THT concentration during odorization was $3\text{--}4 \text{ ml/m}^3$ on the basis of measurement data obtained under very similar working conditions.

On account of increasing complaints and after having trained two colleagues, the subject quit odorizing in 1971. He retired due to persistent respiratory complaints in 1983.

Symptoms and Clinical Course

The patient reported that the intolerably noxious odor during odorization regularly induced nausea, vomiting, eye irritation, ocular and nasal secretion, cough and dyspnea ("chest cramps"). After exposure, the skin of the subject's hands was always reddened and stinging. He developed rhinitis that became chronic, with yellow and viscous secretions.

He underwent paranasal sinus surgery in 1970, but his condition did not improve his condition. Dyspnea initially occurred only during odorization but gradually became persistent during the nights following odorization. After 1970, the patient was frequently unable to work, and repeated hospitalization due to chronic obstructive pulmonary disease (COPD) were necessary. After several months following cessation of this task in 1971, his condition essentially improved.

According to his medical history, therapy with long-acting beta2-sympathomimetics (twice daily) and theophyllin ameliorated his respiratory complaints. Dyspnea with wheezing with stair climbing and at rest, however, persists. Arterial hypertension was diagnosed in 1970 and has required continued treatment. There was no family history of cardiopulmonary diseases.

Results of Clinical Examination

The results of clinical examination are provided in Table I.

Diagnoses

Dermatitis, COPD with reduced $D_{L,CO}$, chronic rhinitis, arterial hypertension, atrial fibrillation.

CASE B

A second male plumber, aged 59, performed natural gas odorization at the same installation from 1970 to 1982.

During the winter, he carried out this activity one to three times per week and up to four times per month during the summer. In 1970, industrial gloves trimmed with leather were introduced as personal protective equipment. When exchanging and opening the buckets, THT splashed frequently, soaking the subject's clothes and depositing on hands, arms, legs, and also on the abdomen. After 1981, rubber gloves and fleece masks were provided and regularly donned. In 1982, tin buckets were replaced by gas bottles. Thus, exposure to THT during the exchange was diminished.

Since 1994, odorization has been performed by an external company in a confined system.

The subject smoked 20 cigarettes per day between 1964 and 1980 and developed intermittent arterial hypertension and cardiac arrhythmia 5 years prior to presentation.

TABLE I. Results of Clinical Examination of Tetrahydrothiophene-Exposed Cases A and B

Results	Case A	Case B
Physical examination	n	Rhinophyma, seborrheic eczema
Blood pressure (mmHg)	140/80 ^a	140/100 ^a
Pulse (/min)	100	72
Heart auscultation	n	n
Lung auscultation	Wheeze, rales	Intermittent wheeze
Orientating neurological investigation	n	n
Laboratory		
Cholesterol (n < 200 mg/dl)	204	243
Triglycerides (n < 200 mg/dl)	74	224
Creatinine (n < 1.2 mg/dl)	0.9	1.1
Lung function testing		
R_{aw} (n < 0.3 kPa/L/s)	0.56	0.37
R_{aw} after β_2 -agonist	0.33	0.31
IGV (% predicted)	82	83
FVC (% predicted)	78	74
FEV ₁ (% predicted)	49	55
FEV ₁ /FVC (%)	50	58
FEV ₁ /FVC (%) after β_2 -agonist	58	72
FEF ₅₀ (% predicted)	27	62
TLC (% predicted)	87	95
(mmHg) at rest	64	57
at 61 W exercise (mmHg)	67	90
$D_{L,CO}$ (% predicted)	59	72
Skin prick testing (with 18 common allergens)	Negative	Negative
ECG	Atrial fibrillation, left ventricular hypertrophy	n
Cycle ergospirometry	61 W, normal blood gases, insufficient increase in heart rate, no indication of myocardial ischemia	125 W, normal blood gases, no indication of myocardial ischemia
Doppler echocardiography	Left atrium 46 mm, left ventricle 52 mm (end-diastolic), left ventricular hypertrophy, reduced ejection fraction (50%), valves were normal	Left atrium 44 mm, left ventricle 68 mm (end-diastolic), left ventricular hypertrophy, reduced ejection fraction (58%), valves were normal
Chest X-ray	Peribronchial thickening, hyperinflation of both lungs, basal pleural fibrosis on the right-hand side	Left ventricular hypertrophy, lungs were normal

n, normal; n.d., not done.

References for spirometry are from Brändli et al., 1996.

^aUnder treatment by angiotensin II receptor antagonist.

Symptoms and Clinical Course

During the odorization process, Case B developed the same symptoms as described in Case A, predominantly nausea, vomiting, headaches, mucosa, irritation, cough, and “chest cramps.” The subject reported having to interrupt his activities frequently to inhale fresh air. He also reported that the backs of his hands showed eczematous, reddened, and scaly skin alterations after direct THT contact in 1970.

From 1972 onwards, the patient suffered from increasing respiratory symptoms, and his nose was persistently blocked by mucus. In addition, a productive, irritable cough with a green-yellow plegm and stomach pain occurred. In addition, he experienced shortness of breath while at work.

After the introduction of gas bottles in 1982, his work-related symptoms decreased. However, productive cough, rhinitis, slight nausea, dyspnea on exertion and when exposed to respiratory irritants persisted.

At presentation, the patient reported a persistent chronic bronchitis and chronic rhinitis. He reported shortness of breath associated with physical stress, damp and cold weather and exposure to environmental tobacco smoke. He was treated with inhalable corticosteroids and short-acting beta2-sympathomimetics as well as theophyllin. He also reported repeated heart palpitations and nosebleeds for the past several years.

Results of Clinical Examination

The results of clinical examination are provided in Table I.

Diagnoses

COPD with mainly reversible bronchial obstruction and reduced D_{LCO} , chronic rhinitis, dermatitis, rhinophyma, seborrheic eczema, hyperlipoproteinemia, arterial hypertension, dilated cardiomyopathy with paroxysmal ventricular and supraventricular arrhythmia by medical history.

DISCUSSION

The estimated level of THT exposure in the workplace was similar to that reported by Krieger [1994], who measured concentrations of 1–13 ml/m³ while decanting THT into containers. The exposed employees of the latter study also developed respiratory disorders and vegetative symptoms. Lung function testing was not reported, however.

Both employees described in our study reported similar complaints (and were experienced by a third co-worker who also performed odorization in the same company but whose medical records are not available). They suffered from work-related neurologic symptoms, skin and mucosa irritation, rhinitis, initial asthmatic symptoms that developed

into COPD with impaired lung function and reduced lung diffusion capacity. In addition, hypertension in combination with intermittent ventricular and supraventricular arrhythmia in one case, and in combination with atrial fibrillation and dilated cardiomyopathy in the second case, was present without evidence of coronary artery disease or valvular dysfunction. There was neither family history nor evidence of a pre-existing competitive neurological or cardiopulmonary disease, allergy, immunodeficiency syndrome, α_1 -antitrypsin deficiency, or kidney or liver disease. We asserted in the expert opinions that COPD had developed in both patients as an occupational disease. The statutory accident insurance institution accepted this diagnosis and granted compensation.

In the light of severe CNS disorders experimentally elicited by high TNT concentrations in animals [Pennwalt Corporation, 1975, 1985, 1986; Mikhalets, 1964], nausea, vomiting, headaches, loss of appetite reported by the exposed workers likely represent transient neurotoxic effects. The temporal relation between exposure and occurrence of skin and respiratory symptoms as well as the initial improvement after exposure termination favored the development of dermatitis, rhinitis, and chronic obstructive airway diseases due to THT. Whether there is a causal relation between THT exposure on the one hand and arterial hypertension and cardiac arrhythmia on the other hand could not be clarified, since other causes could not be definitively excluded. A causative association is suggested by the fact that both subjects developed these disorders after long-term high THT contact and by lethal ventricular arrhythmia observed in THT-exposed cats to which adrenalin was administered. In this context it is interesting that common industrial solvents have also been reported to induce cardiac arrhythmia [Reinhardt et al., 1973; Kobayashi et al., 1987] as well as arterial hypertension [Kotseva and Popov, 1998].

TLVs of THT have neither been stipulated in the USA nor in most other countries. According to the latest data on hazardous substances issued by the Senate Commission of the Deutsche Forschungsgemeinschaft, the MAK (maximum workplace concentration) of THT is fixed at 50 ml/m³ [Deutsche Forschungsgemeinschaft, 2007]. THT exposure tests in rats indicating mucosa irritations at doses >50 ml/m³ served as the scientific basis [Greim, 2006].

The Rijksinstituut voor Volksgezondheid en Milieu (RIVM) evaluated the non-cancer toxicity data of THT and derived a tolerable air concentration of 0.18 ml/m³ based on an adjusted NOAEL of 180 ml/kg-day for effects on adrenal glands [Glaser, 1990] of rats and using an uncertainty factor of 1000 (National Institute of Health, 2009).

In spite of missing THT workplace measurement values in our cases, we can assume exposure levels comparable to those obtained by ambient measurements under similar conditions in the clinical report of Krieger [1994]. Our findings as well as those of Krieger [1994] indicate clinical

effects to occur in humans at lower THT concentrations than in rats. In our opinion, the observed dose–effect relation in rats cannot be transferred to human beings since humans are obviously more sensitive to THT than rodents. A more detailed investigation and evaluation of the literature should be performed in order to establish a scientific and health-based TLV. We also recommend that all employees currently or formerly exposed to THT under comparable conditions be offered screening for cardiopulmonary diseases. Furthermore, we suggest regular surveillance examinations of currently exposed employees.

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