# POSSIBLE BIOLOGICAL MECHANISMS OF SUDDEN SNIFFING DEATH SYNDROME DUE TO TOLUENE EXPOSURE

## Toluen Maruziyeti Sonucu Gelişen Uçucu Madde Koklamaya Bağlı Ani Ölüm Sendromunun Muhtemel Biyolojik Mekanizmaları

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## ABSTRACT

Sudden sniffing death syndrome due to toluene exposure is an outcome of the progressive social problem of intentional substance inhalation abuse. There is limited evidence about the biological mechanisms of toluene-induced sudden death, although toluene exposure is prevalent as a volatile solvent used in industrial settings. Toluene is known to possess toxic effects on many organs, most dramatically on the heart. Sudden death may result directly from ventricular tachyarrhythmias and severe bradycardia due to the cardiac toxicities of toluene. Toluene may also result in cardiomyopathy, myocarditis, and myocardial infarction, all of which are known to be associated with sudden death. In addition to its toxicity on the heart, this solvent is also toxic to the lungs, kidneys, nervous system, and bone marrow, which may contribute to the mechanism of sudden sniffing death due to toluene exposure. For these reasons, toluene-induced sudden death is discussed in this paper as a complex combination of the toxicities of toluene to the heart and other organs.


**Key words:** Sudden death, toluene.


## ÖZET

Toluene bağlı ani koklama ölüm sendromu; toluen solunmasının ölümcül bir sonucudur ki bu durum giderek büyüyen bir sosyal sorundur. Toluen'e maruziyet stimülan ajan olarak ya da endüstride kullanımı şeklinde yaygın olsa da toluene bağlı ani ölümün biyolojik mekanizmaları hakkında sınırlı bilgi vardır. En dramatiği kalp üzerine olmak üzere toluenin birçok organ üzerine toksik etkisinin olduğu bilinmektedir. Ani ölüm toluenin kalp üzerine doğrudan toksik etkileri sonucu gelişen ventriküler taşiaritmi ya da ciddi bradikardi neticesinde doğrudan gelişebilir. Bu madde aynı zamanda kardiyomyopati, miyokardit ve miyokard infaktüsü gibi ani ölümle yakından ilişkili hastalıklara neden olabilir. Toluenin akciğerler, böbrekler, sinir sistemi ve kemik iliği gibi toluene bağlı ani ölüm mekanizmasına katkıda bulanabilecek organlar üzerine toksik etkileri vardır. Sonuç olarak, bu derlemede toluene bağlı ani ölümün maddenin kalp ve birçok organ üzerine toksik etkilerin karmaşık bir kombinasyonu sonucu geliştiği tartışılmıştır.


**Anahtar kelimeler:** Ani ölüm, toluen.

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## INTRODUCTİON

Industrial exposure is a common pathway of toluene toxicity in many sectors. Since the 1960s, volatile inhalants have also become increasingly popular as drugs of abuse among children and young adults. Because volatile inhalants are relatively inexpensive and often included in common household products, paint thinner and adhesives are now among the most widely used stimulants in Turkey and many developing countries. In a recent study, the prevalence of paint thinner and adhesive abuse was 73% among homeless children and 5% among second-grade students in high schools in Istanbul, the largest metropolitan area of Turkey. This recent data has shown an increase in the number of volatile agent addicts. In the Western World (e.g., Britain or the United States), 5-20% of children have experimented with inhalants, pointing to volatile agent abuse as a worldwide problem (4,5).

Sudden sniffing death syndrome is the most dramatic outcome of volatile agent inhalation. As many as 50% of inhalant-related deaths are asssociated with sudden sniffing death syndrome, which occurs due to the cardiac toxicity of volatile agents (6-8). There has been a steady increase in the number of deaths per year occurring from volatile substance abuse (9). We discuss possible biological mechanisms of sudden death associated with toluene exposure in this review article.

## DISCUSSION

In victims of sudden sniffing death syndrome, no pathologic findings were generally detected at autopsy (7). Therefore, sudden death is regarded as a prompt event that is mainly related to ventricular tachyarrhythmias and severe bradycardia due to the cardiac toxicity of volatile agents. Aerosols are more frequently associated with sudden death. Solvents are known as a relatively weak agent for inducing sudden sniffing death syndrome. It is suggested that sudden sniffing death syndrome due to toluene exposure is a rare phenomenon.

Different types of paint thinners and adhesives sold in Turkey contain 50-70% and 35-40% toluene, respectively. Toluene effects many organs in the body, especially the central nervous system and heart. Small doses of toluene can rapidly lead to euphoria and other disturbances of behaviour. Moderate doses of the agent may also induce delusions and hallucinations. Higher doses may produce life-threatening effects, such as convulsions and coma. Death may occur due to its direct cardiac or central nervous system toxicity or indirectly from, for example, inhalation of vomit, accidental trauma, and asphyxia (10).

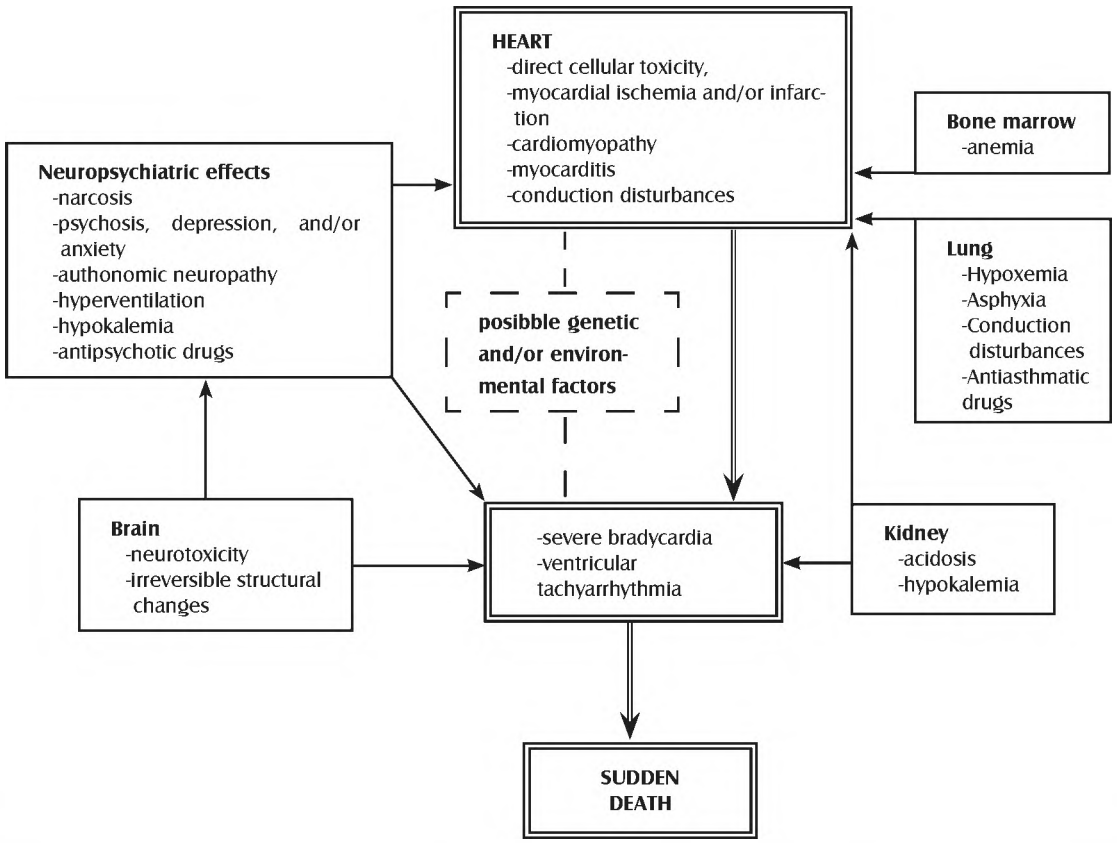
Toluene exposure has resulted in chronic damage to the heart, lungs, kidneys, liver, peripheral nerves, and brain. (11,12). Toluene is oxidized gradually by cytochrome P450-dependent monooxygenase after its systemic absorption through the lungs and skin. Consequently, reactive oxygen species (ROS) are produced. ROS result in cellular toxicity to many organs (13). Paint thinner inhalation is known to increase lipid peroxidation and induction of antioxidant enzymes. Hool (14) noted that a common source of solvent-inducible oxidants may be located in mitochondria where the respiratory chain operates. Garbe et al. (15) discussed that ROS have been considered deleterious to cell function and there is good evidence to suggest that they play a role in the pathophysiology of a number of cardiac disease states, such as atherosclerosis, ischaemia, cardiac hypertrophy, and hypertension. Akar et al. (16) related collapse and instability of the mitochondrial inner membrane potential to mitochondrial ROS-induced ROS release and highlight the mitochondrial membrane as a new therapeutic target for prevention of arrhythmia. Toluene as a lipophilic solvent disturbs cellular membrane integrity, electrophysiology of the cellular membrane and inner membrane of mitochondria, and leads to reversible or irreversible cellular damage.

At higher doses (for example, 200 ml of paint thinner ingestion), tissue damage that effects many organs may be prompt and fatal (17). Moderate- or low-dose exposure of toluene may result in ventricular extrasystoles, bundle branch block, sinus bradycardia and A-V block (18-20), myocardial ischemia or infarction (21-24), cardiomyopathy (20,25), acute myocarditis (26), and ventricular tachyarrhythmias that are often ignored. These toxicities are closely related to sudden death. Coincidental allergic asthma, bronchitis, nephropathy, encephalopathy, neuropsychiatric diseases, and anemia contribute to the fatal outcome (Figure 1).

Toluene renders the heart susceptible to endogenous catecholamines, such that sudden alarm or exercise may precipitate sudden death (9). It also induces evident ischemia due to vasospasm, which may play an important role in the development of serious cardiac rhythm problems. In the case of myocardial infarction related to toluene exposure, recurrent ventricular fibrillation attacks resistant to defibrillation and antiarrhythmic treatment were often reported. Coexisting electrolyte abnormalities caused by renal toxicity of this substance may also contribute to the development of fatal arrhythmias (27).

In two cases of toluene-induced cardiomyopathy, left ventricular systolic function largely or completely returned to normal after the substance abuse ended (20). It could be argued that the toxic effects of toluene on the heart muscle may be reversible. In the literature, the damage or segmental wall motion abnormalities of the myocardium were usually reversible among the cases of toluene-induced myocardial infarction. Toluene is suggested to result in coronary vasospasm and functions of the myocardium returned to patently normal when the spasm was over. Recurrent non-Q-wave infarction associated with toluene inhalation obviously resulted in permanent cardiomyopathy (23). Anemia due to toluene-induced bone marrow toxicity may also contribute to induction of myocardial ischemia.

**Figure 1: Basic Schematic Representation of Possible Biological Mechanisms of Sudden Death Sniffing Death Syndrome Associated with Toluene Exposure.**




**Note:** Double-line boxes and arrows show the main mechanism of toluene-induced sudden death. The dotted-line box is a possible a contributor; but needs further investigations. Other boxes and single-line arrows explain possible cardiovascular effects of other organ damage due to toluene exposure, which are suggested as other contributors to the main mechanism of toluene-induced sudden death.

The lungs are another organ effected by toluene, both directly during sniffing of toluene vapour and indirectly after systemic absorption of the agent. Isocyanates such as toluene diisocyanate are regarded as the most common cause of occupational asthma, with more than 100,000 workers in the U.S. exposed annually and 5-10% of these developing asthma (28). An 18-year-old student with a history of asthma accidentally inhaled organic solvent during a class and complained of immediate cough and dyspnea that worsened over the course of several hours (29). This case presented with severe respiratory distress, hypoxemia, and marked pulmonary hyperinflation as a result of mucus plugging, regarded as a complication of acute inhalation injury or acute severe asthma. In another study, a 43-year-old car painter who died within 1 hour after exposure to a polyurethane paint in the workplace is reported (30). Histologic examination showed diffuse mucus plugging and intense inflammation of the bronchioles. There are also distinct pathologic findings in the conduction system of young adults with a history of bronchial asthma who die suddenly. It is hypothesized that bronchial asthma affects the conduction system in some patients (31). The significant findings include the appearance of a markedly fragmented bundle and changes in the sinoatrial node that are not found in normal healthy young adults. We do not know whether toluene-induced asthma has similar effects to the conduction system, but toluene-induced lung toxicity may predispose the individual to serious arrhythmias and sudden death due to mucus plugging of bronchioles, severe respiratory distress, hypoxemia, antiasthmatic drugs, and changes in the conduction system of the heart.

Renal toxicity of toluene may also contribute to sudden death. Toulene may cause acid-base imbalances, acute renal failure, Fanconi's syndrome, and renal tubular acidosis. In an experimental study involving toluene-treated rats, the weights of the kidneys diminished by 13%. Gupta et al. (32) described a 38-year-old male who developed acute oliguric renal failure following repeated glue sniffing for about 8 hours. Clinical and laboratory findings of this case supported the diagnosis of acute toxic tubular necrosis causing acute renal failure. Batlle et al. (33) documented the occurrence of hypokalemia and hyperchloremic metabolic acidosis due to the distal form of renal tubular acidosis in five individuals addicted to toluene sniffing.

Toluene induces structural changes in the brain in solvent abusers. MR images revealed white matter lesions in 46%, atrophic dilatation of ventricles and sulci in 27%, and thalamic hypointensity in 20% of the patients who had abused toluene-containing solvents for longer than 4 years (34). The deposition of iron due to demyelination and axonal loss is the most probable mechanism for the thalamic hypointensity found in solvent abusers. The brain partially controls the functions of many organs such as the heart and adrenal glands. The malfunction of the brain in toluene addicts may possibly contribute to the mechanism of sudden death (35,36). Neuropsychiatric side effects of toluene may also increase the risk for sudden death. Some psychiatric conditions such as anxiety, depression, delirium, or psychosis are regarded as transient risk factors for sudden cardiac death (37). Chronic inhalation of toluene-based adhesives can produce permanent paranoid psychosis (38,39). Dementia and depression are some of the other neuropsychiatric adverse effects of toluene. Anxiety and depression are well-known risk factors for myocardial infarction and sudden death. Clinical depression may be associated with a higher risk of cardiac arrest independently of established coronary heart disease risk factors (40). Psychosis may result in hypokalemia due to hyperventilation and adrenergic discharge, which may contribute to the induction of ventricular tachyarrythmia (41). A prolonged corrected QT interval due to antipsychotics and hypothermia in psychiatric patients should also be regarded as the mechanism between toluene-induced psychosis and sudden unexplained death (42,43). Toluene may also effect the autonomic nervous system (central or peripheral) that is essential for maintaining appropriate cardiac rhythm.

Toluene in similar doses may cause cardiomyopathy in one individual but nothing in others, as frequently seen in our experience. Therefore, there might be some genetic and environmental factors that increase toluene's toxicity or have an additive effect to its toxicity. If a person has an increased risk of sudden death (e.g., mutations in genes of cardiac ion channels), it should be expected that toluene exposure could have an additive effect. It has already been discussed that co-administered antiasthmatics, antipsychotics, and narcotic agents may increase the risk for sudden death. Because abused inhalants are common in household products and are relatively inexpensive, they are accessible to children who are too poor or too young to access other drugs. However, inhalant abuse appears to be a gateway phenomenon among younger adolescents. Children who abuse inhalants early in life are more likely to use other illicit drugs later in life (44,45). They may sometimes inhale toluene concurrent with abuse of cannabis, heroin, amphetamines, or cocaine, which may increase the risk of sudden death.

In conclusion, toluene-induced sudden death is not purely associated with its isolated cardiac toxicity. Toluene exposure may result in various organ toxicities and many types of cardiac involvement, the combinations of which may induce sudden death. Some genetic and environmental factors may also contribute to the pathogenesis of sudden sniffing death syndrome due to toluene exposure. Further research is needed to make more definitive conclusions.

## REFERENCES


1- Ögel K, Yücel H, Aksoy A: İstanbul'da sokakta yaşayan çocukların özellikleri. Yeniden Bilimsel Araştırma Raporları. Yayın no: 7. İstanbul, 2004.

2- Öğel K, Taner S, Eke C, Erol B: İstanbul'da Onuncu Sınıf Öğrencileri Arasında Tütün, Alkol ve Madde Kullanım Yaygınlığı Raporu. Yeniden Yayın no. 15. İstanbul, 2005.

3- Öğel K, Tamar D: Ruhsal Bozukluklar Epidemiyolojisi: Alkol ve madde kullanım bozuklukları epidemiyolojisi. Ege Psikiatri Sürekli Yayınları, 2000, p 124.

4- Davies B, Thorley A, O'Connor D: Progression of addiction carriers in young adult solvent misusers. Br Med J (Clin Res Ed) 1985;290:109-110.

5- McGarvey EL, Clavet GJ, Mason W, Waite D. Adolescent inhalant abuse: environments of use. Am J Drug Alcohol Abuse 1999;25:731-41.

6- Flanagan RJ, Ives RJ. Volatile substance abuse. Bull Narc 1994;46:49-78.

7- Bass M. Sudden sniffing death. JAMA 1970;212: 2075-9.

8- Adgey AA, Johnston PW, McMechan S. Sudden cardiac death and substance abuse. Resuscitation 1995; 29:219-21.

9- Monitoring the future survey release. Smoking among teenagers decreases sharply and increase in ecstasy use slows. U.S. Department of Health and Human Services HHS News; 2001.

10- Inhalant abuse. American Academy of Pediatrics, Committee on Substance Abuse and Committee on Native American Child Health. Pediatrics 1996; 97:420-3.

11- Carabez A, Sandoval F, Palma L: Ultrastructural changes of tissues produced by inhalation of thinner in rats. Microsc Res Tech 1998; 40:56-62.

12- Meadows R, Verghese A. Medical complications of glue sniffing. South Med J 1996; 89:455-62.

13- Halifeoglu I, Canatan H, Ustundag B, Ilhan N, Inanc F. Effect of thinner inhalation on lipid peroxidation and some antioxidant enzymes of people working with paint thinner. Cell Biochem Funct. 2000;18:263-7.

14- Hool LC. Reactive oxygen species in cardiac signalling: from mitochondria to plasma membrane ion channels. Clin Exp Pharmacol Physiol 2006;33:146-51.

15- Garbe TR, Yukawa H. Common solvent toxicity: autoxidation of respiratory redox-cyclers enforced by membrane derangement. Z Naturforsch [C] 2001; 56:483-91.

16- Akar FG, Aon MA, Tomaselli GF, O'Rourke B. The mitochondrial origin of postischemic arrhythmias.

J Clin Invest 2005;115:3527-35.
17- Akisu M, Mir S, Genc B, Cura A. Severe acute thinner intoxication. Turk J Pediatr 1996; 38:223-5.
18- Aono J, Takimoto E, Komatsu T, Takeda A, Ueda W, Hirakawa M. Anesthetic care of a patient intoxicated with thinner. Masui 1990;39:388-90.
19- Zee-Cheng CS, Mueller CE, Gibbs HR Toluene sniffing and severe sinus bradycardia. Ann Intern Med 1985;103:482.
20- Vural M, Ogel K. Dilated Cardiomyopathy Associated with Toluene Abuse. Cardiology 2006;105:158-161.
21- Cunningham SR, Dalzell GW, McGirr P, Khan MM: Myocardial infarction and primary ventricular fibrillation after glue sniffing. Br Med J (Clin Res Ed) 1987;294:739–740.
22- Carder JR, Fuerst RS. Myocardial infarction after toluene inhalation. Pediatr Emerg Care 1997; 13:117-119.
23- Hussain TF, Heidenreich PA, Benowitz N. Recurrent non-Q-wave myocardial infarction associated with toluene abuse. Am Heart J 1996; 131:615-616.
24- Gustavsson P, Plato N, Hallqvist J, et al. A population-based case-referent study of myocardial infarction and occupational exposure to motor exhaust, other combustion products, organic solvents, lead, and dynamite. Stockholm Heart Epidemiology Program (SHEEP) Study Group. Epidemiology 2001;12:222-8.
25- Wiseman MN, Banim S: 'Glue sniffer's' heart? BMJ (Clin Res Ed) 1987; 294:739.
26- Knight AT, Pawsey CG, Aroney RS, Lawrence JR, Jones DB, Newland RC: Upholsterers' glue associated with myocarditis, hepatitis, acute renal failure and lymphoma. Med J Aust 1991;154:360-362.
27- Kirk LM, Anderson RJ, Martin K. Sudden death from toluene abuse. Ann Emerg Med 1984;13:68-69.
28- Tee RD, Cullinan J, Burge SP, Newman Taylor AJ. Specific IgE to isocyanates: a useful diagnostic role in occupational asthma. J Clin Immunol 1998;101:709-15.
29- Koga T, Kawazu T, Iwashita K, Yahata R. Pulmonary hyperinflation and respiratory distress following solvent aspiration in a patient with asthma: expectoration of bronchial casts and clinical improvement with high-frequency chest wall oscillation. Respir Care 2004; 49:1335-8.
30- Fabbri LM, Danieli D, Crescioli S, Bevilacqua P, Meli S, Saetta M, Mapp CE. Fatal asthma in a subject sensitized to toluene diisocyanate. Am Rev Respir Dis 1988; 137:1494-8.
31- Bharati S, Lev M. Conduction system findings in sudden death in young adults with a history of bronchial asthma. J Am Coll Cardiol 1994; 23:741-6.
32- Gupta RK, van der Meulen J, Johny KV. Oliguric acute renal failure due to glue-sniffing. Case report. Scand J Urol Nephrol 1991; 25:247-50.
33- Batlle DC, Sabatini S, Kurtzman NA. On the mechanism of toluene-induced renal tubular acidosis. Nephron 1988; 49:210-8.
34- Aydin K, Sencer S, Demir T, Ogel K, Tunaci A, Minareci O. Cranial MR findings in chronic toluene abuse by inhalation. Am J Neuroradiol 2002; 23:1173-9.
35- Paul M, Schafers M, Kies P, Acil T, Schafers K, Breithardt G, Schober O, Wichter T. Impact of sympathetic innervation on recurrent life-threatening arrhythmias in the follow-up of patients with idiopathic ventricular fibrillation. Eur J Nucl Med Mol Imaging 2006;33:866-70.
36- Issa ZF, Zhou X, Ujhelyi MR, Rosenberger J, Bhakta D, Groh WJ, Miller JM, Zipes DP. Thoracic spinal cord stimulation reduces the risk of ischemic ventricular arrhythmias in a postinfarction heart failure canine model. Circulation 2005; 111:3217-20.
37- Fricchione GL, Vlay SC. Psychiatric aspects of patients with malignant ventricular arrhythmias. Am J Psychiatry. 1986;143:1518-26.
38- Byrne A, Kirby B, Zibin T, Ensminger S. Psychiatric and neurological effects of chronic solvent abuse. Can J Psychiatry. 1991; 36:735-8.
39- Goldbloom D, Chouinard G.Schizophreniform psychosis associated with chronic industrial toluene exposure: case report. J Clin Psychiatry 1985; 46:350-1.
40- Empana JP, Jouven X, Lemaitre RN, Sotoodehnia N, Rea T, Raghunathan TE, Simon G, Siscovick DS. Clinical depression and risk of out-of-hospital cardiac arrest. Arch Intern Med 2006;166:195-200.
41- Hatta K, Takahashi T, Nakamura H, Yamashiro H, Asukai N, Yonezawa Y. Hypokalemia and agitation in acute psychotic patients. Psychiatry Res 1999; 86:85-8.
42- Lindstrom E, Farde L, Eberhard J, Haverkamp W.QTc interval prolongation and antipsychotic drug treatments: focus on sertindole. Int J Neuropsychopharmacol 2005; 8:615-29.
43- Young DM. Risk factors for hypothermia in psychiatric patients. Ann Clin Psychiatry. 1996; 8:93-7.
44- Bennett ME, Walters ST, Miller JH, Woodall WG. Relationship of early inhalant use to substance use in college students. J Subst Abuse 2000;12: 227-40.
45- Young SJ, Longstaffe S, Tenenbein M. Inhalant abuse and the abuse of other drugs. Am J Drug Alcohol Abuse 1999;25:371-5.