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N-Nitrosodiethanolamine in Synthetic Cutting Fluids: A Part-Per-Hundred Impurity

Abstract. N-*nitrosodiethanolamine has been found to be present at a concentration of 0.02 to 3 percent in several brands of synthetic cutting fluids. Its identity was confirmed by three independent techniques: (i) by measuring the retention times on two different high-performance liquid-chromatography columns, (ii) by dehydration to* N-*nitrosomorpholine, and (iii) by preparation of the* O-*methyl ether derivative.*

Cutting fluids are widely used to reduce the temperature of the metal-tool interface during metal cutting and grinding. The majority of cutting fluids used in the United States are synthetic; they contain up to 45 percent triethanolamine and 18 percent sodium nitrite and have *p*H values in the range 9.0 to 11.0. Lijinsky *et al.* (*1*) demonstrated that triethanolamine could readily be nitrosated to form *N*-nitrosodiethanolamine (NDElA). Using a model system, Zingmark and Rappe (*2*) recently showed that triethanolamine would be expected to undergo in vivo nitrosation under simulated gastric conditions. *N*-Nitrosodiethanolamine is of interest because it has been shown to produce liver tumors in rats (*3*). We report here on its presence in relatively larger amounts as an impurity in commercial cutting fluids.

Cutting fluids were obtained commercially in the Boston area. Authentic NDElA was prepared as described by Druckrey *et al.* (*3*). The identity of the compound was confirmed by chemical ionization mass spectrometry and electron impact high-resolution mass spectrometry. A high-pressure liquid chromatograph–thermal energy analyzer (HPLC-TEA) was constructed from a high-pressure pump (Waters model 6000A), an injector (Waters model U6K), a column (Waters), and a TEA detector (Thermo Electron model 502) (*4, 5*).

Cutting fluid was chromatographed as purchased without any treatment on a μ Porasil column (Waters), using as a solvent system 50 percent hexane and 50 percent acetone at a flow rate of 2 ml/min. A peak eluting at the retention time of NDElA was determined. Since no cleanup was used, the possibility of artifact formation was discounted. Because crude fluid rapidly degraded the column, routine analyses were carried out after first extracting with ethyl acetate in the presence of magnesium sulfate. The extract was filtered through sodium sulfate and then injected onto the HPLC-TEA (*6*). The results are presented in Table 1.

In order to confirm the identity of the peak eluting at the retention time of NDElA, the compound was isolated (*7*) and studied by three independent techniques.

1) High-pressure liquid chromatography. The isolated sample was injected onto an HPLC-ultraviolet spectrometer or HPLC-TEA by using either a μ Bondapak NH_2 or a μ Porasil column (*8*). With both systems we always observed a material eluting at the same retention time as authentic NDElA.

Table 1. Concentration of *N*-nitrosodiethanolamine in several brands of synthetic cutting fluids.

Brand	NDElA (%)
A	2.99
B	1.04
C	0.42
D	0.25
E	0.18
F	0.06
G	0.06
H	0.02

2) Dehydration. The isolated sample, when dehydrated with concentrated sulfuric acid (96 percent) at 155°C for 2.5 hours, yielded *N*-nitrosomorpholine as the dehydration product. *N*-Nitrosomorpholine was detected by combined gas chromatography and high-resolution mass spectroscopy (*9*). The isolated sample did not give an *N*-nitrosomorpholine peak before dehydration.

3) Derivative formation. The *O*-methyl ether derivative of the isolated sample was prepared by methylation with methyl iodide, with sodium hydride as a catalyst (*10*). The methylated sample was distilled and the distillate extracted with methylene chloride. The concentrated extract was then introduced into a gas chromatograph fitted with a Coulson electrolytic conductivity detector in the nitrogen mode (*11*). The presence of the NDElA derivative in the isolated sample was confirmed when the retention time was compared with that of the *O*-methyl ether derivative of authentic NDElA.

The cutting fluids that we tested represent only a small fraction of the total number of commercial brands that are available. On the basis of results reported here, we expect that most cutting fluids that contain triethanolamine or diethanolamine and nitrite as additives will be contaminated with NDElA. To assess the magnitude of the problem, we recommend screening all brands of synthetic cutting fluids.

The *N*-nitrosamine content of cutting fluids is about 40 times higher than the nitrosamine contamination in some herbicides (*12*) and 10^7 times higher than that found in foodstuffs preserved with nitrites (*13*). Persons who use cutting fluids could well be exposed to nitrosamine. Even though the fluids are diluted 10 to 100 times before use, the amount of the nitrosamine present is such that it may pose a carcinogenic hazard to all users.

In the past 30 years, cutting oils have been frequently cited as related to cancer of the scrotum among machine operators (*14, 15*). Several cutting oils were found to be carcinogenic to laboratory animals (*15, 16*), and compounds such as polycyclic aromatic hydrocarbons and heterocyclic compounds were believed to be the carcinogens (*17*). Over the past 20 to 30 years, synthetic formulations have replaced the original mineral oils. Almost all of the "cutting oils" used today are of the synthetic variety. The synthetic cutting fluids described here have been in widespread use for about 20 years and, because of the 20-year latency period expected for human cancer (*18*), we would not expect cancer incidence among machinists to be related to NDElA. However, machinists may have been exposed to relatively large amounts of NDElA by skin absorption and inhalation. We suggest that epidemiological studies be initiated to screen workers who have been subjected to NDElA for prolonged periods. Until now, *N*-nitrosamines have not been directly associated with human cancer because no population groups had been identified that were inadvertently exposed. Cutting fluid users have the dubious honor of being the first such population group to be identified.

Note added in proof: Zingmark and Rappe initially reported NDElA to be absent from grinding fluid (*2*). Since submission of this manuscript, we were informed by Rappe of a second manuscript (*19*) reporting the presence in grinding fluid stored for 4 to 6 months of a compound which was claimed to be NDElA.

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6. The recovery of NDElA after this procedure was 100 percent.
7. A 0.1-ml portion of cutting fluid (brand C) was extracted with 30 ml of diethyl ether or ethyl acetate in the presence of 10 g of magnesium sulfate. The extract was filtered through 20 g of sodium sulfate. The filtrate was concentrated with a stream of nitrogen to approximately 300 μl and loaded onto a silica gel column (1 by 5 cm), which was washed with 50 ml of diethyl ether and then eluted with 50 ml of ethyl acetate. The eluate was concentrated to approximately 300 μl as the final isolated sample. An aqueous solution containing 5 percent each of sodium nitrite and triethanolamine was treated by the same isolation procedure used for the cutting fluid. No artifact formation of NDElA was found during the procedure.
8. The solvent system was 3 percent methanol and 97 percent methylene chloride for the μ Bondapak NH_2 column, and 30 percent acetone and 70 percent hexane for the μ Porasil column. The flow rate for both columns was 2 ml/min.
9. The column (6 feet by ⅛ inch) was packed with 5 percent Carbowax 20 M on 100- to 200-mesh Chromosorb W High Performance and used isothermally at 180°C. The flow rate of helium carrier gas was 25 ml/min. The mass spectrometer was operated to monitor the molecular ion of *N*-nitrosomorpholine at a resolution of 10,000.
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11. The column was packed with 25 percent Carbowax 20 M containing 2 percent NaOH on 80- to 100-mesh Chromosorb P. The temperature of the column was maintained isothermally at 140°C for 3 minutes and then programmed to 180°C at a rate of 10°C per minute. The flow rate of the helium carrier gas was 25 ml/min.
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Perception of Impossible Limb Positions Induced by Tendon Vibration

Abstract. *When the wrist flexor muscle is vibrated and the wrist is passively extended to a position close to its anatomical limit, the hand is felt to be bent to a position about 29° beyond its maximum operating range. The mechanism of position sense must in this case be operating on the basis of extrapolation. Ambiguity of sensed position can occur in this situation. Some subjects, when opposing the vibration-induced contraction of biceps, report experiencing multiple forearms.*

Until recently, position sense in limbs was thought to be due solely to the receptors associated with the joint capsule and pericapsular tissue (*1*). However, evidence now strongly suggests a role for muscle receptors, especially the primary endings of muscle spindles (*2*). In this report I present evidence that vibration of muscle tendons can result in errors of position sense as great as 54° when the muscle is passively stretched. Furthermore, the size of this effect is not restricted by the anatomically given limits of flexion and extension.

Cat spindle primary endings are highly sensitive to periodic stretch of small amplitude while secondary endings are not (*3*). In humans, vibration of a tendon causes a predictable increase in the contractile activity of the agonist, caused by autogenous reflex excitation of the alpha motoneurons and reciprocal inhibition of the antagonist. This leads to involuntary movement (*4*). When this movement is stopped by an external agent, the subject reports a persistent illusion of movement in the direction appropriate to extension of the vibrated, and contracting, muscle. This is associated with an error of position sense, also in the direction of extension, the size of which has been reported as being between 5.5° (*5*) and 8° (*2*) when the biceps tendon is vibrated at 100 hertz. McCloskey (*5*) argues that these position signals are not merely the integration of those responsible for the persistent movement illusion, for the size of the position error does not increase with vibration time. Furthermore, procedures that lower or abolish the movement illusion do not similarly affect the size of the position error. This makes the existence of the position illusion of considerable theoretical importance, for it implies that some of the afference from the muscles could be used by the brain as a source of positional information, as distinct from the notion that vibration merely biases position analysis by virtue of the volume of movement information.

Some properties of the muscularly derived position mechanism were studied in right-handed subjects 6 to 40 years of age. The majority were university students and faculty. The apparatus consisted of a vibrator with a piston 15 mm in diameter which was driven sinusoidally at 80 hertz with stroke, under load, of 2 mm. This piston was applied to various sites on the left arm. Objective measurement of the position of the left wrist or hand was achieved by asking the subject, whose vision was occluded, to make a mark with a pen held in the right hand on a vertically mounted Plexiglas sheet adjacent to the left arm. This task used only the position sense of the two arms. Precise localization of wrist or hand of the experimental arm was aided by the experimenter touching one or the other with a slender pointed rod. The effect of