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Forensic Science International  
87 (1997) 219–237

**Forensic  
Science  
International**

## A possible chemical explanation for the events associated with the death of Gloria Ramirez at Riverside General Hospital

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Received 17 March 1997; accepted 10 April 1997

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### Abstract

The events associated with the death of Gloria Ramirez at Riverside General Hospital on 19 February 1994 have been portrayed as a major medical mystery. A potential chemical explanation for this incident has been developed. The hypothetical scenario depends upon the oxidation of a common solvent, dimethyl sulfoxide, through dimethyl sulfone to dimethyl sulfate. The latter compound is a volatile and highly toxic agent that can be quite hazardous to humans in small amounts. It is also environmentally nonpersistent. Much of the mystery surrounding the circumstances at the hospital may be explainable if this postulated metabolic pathway took place at the time of the emergency room incident. Although dimethyl sulfate was not detected in any analyses pertinent to this event, there are plausible scientific explanations to account for that fact. The sulfate anion, a hydrolysis product of dimethyl sulfate, was measured at an appreciably elevated concentration in Ramirez' blood. The descriptions of the symptoms of the hospital-staff victims appear quite consistent with dimethyl sulfate exposures. This paper attempts to make some sense of the reported data and eyewitness accounts, and perhaps provide new insight for any future research that could further explain this reported occurrence of toxic exposure. © 1997 Elsevier Science Ireland Ltd.

*Keywords:* Toxic incident; Chemical scenario; Riverside General Hospital; Emergency Room 'mystery fumes'

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## 1. Background

At approximately 7:50 p.m. on 19 February 1994, Riverside Fire Department personnel and an ambulance arrived at the home of Gloria Ramirez, a noncompliant patient with terminal cervical cancer. Ramirez was in acute distress, with an irregular heartbeat and difficulty breathing. Further, she had a recent history of nausea and vomiting over the previous several days. In the ambulance, Ramirez was placed on monitor, administered oxygen, and started on an IV. The ambulance arrived at the Riverside General Hospital Emergency Room (ER) at approximately 8:15. Ramirez was semiconscious, sluggishly responsive, with shallow breathing and rapid heartbeat. Ramirez' condition deteriorated, and a full-code cardiopulmonary resuscitation was begun by the ER staff.

Patient ventilation was conducted by Maureen Welch, a respiratory therapist. Nurse Susan Kane started a second IV and a venipuncture, drawing blood with a 20–30 ml syringe. Kane and other ER personnel noted an ammonia-like odor that appeared to emanate from Ramirez. Kane then fainted. Dr. Julie Gorchynski assumed Kane's position, smelled the syringe, and noted the presence of uncharacteristic white or manilla crystals in the blood. Dr. Humberto Ochoa, Chair of the Department of Emergency Medicine, also noted white crystals in the blood in the syringe. Gorchynski lost consciousness and exhibited intermittent respiratory distress and convulsions. Welch and several other ER staff also became ill, and Ochoa then ordered evacuation of the ER.

Medical care on Ramirez was continued by Ochoa and others; during the resuscitation, she was intubated, given additional medications, and cardioverted and defibrillated multiple times. [The medications included, but were not limited to, Ativan (lorazepam), Bretylium (bretylum tosylate), Versed (midazolam), Valium (diazepam), lidocaine, calcium, magnesium and bicarbonate.] Ramirez failed to respond and was pronounced dead by Ochoa at 8:50.

The ER evacuation was completed, and Riverside General Hospital declared an internal disaster and was placed on emergency diversion, redirecting all ambulance services to other hospitals. Teams from the City of Riverside Fire Department and a Hazardous Materials (HAZMAT) crew arrived, and the hospital administrator, safety officer, and Riverside Coroner also arrived on scene. A total of nearly two dozen hospital workers were affected, and six of the ER staff were hospitalized at other facilities for medical treatment. At approximately 11:00, HAZMAT entered the ER and conducted air testing for common hazardous gases. The results were negative.

Following a planning meeting involving HAZMAT, a City of Riverside Environmental Health Resource Team, hospital administration, and the Coroner, HAZMAT conducted decontamination procedures in the ER. Ramirez was placed within a double-sealed bag, in an airtight casket, and moved to the hospital morgue. HAZMAT released the ER to the hospital staff at approximately 3:05 a.m. on 20 February 1994, and the hospital Environmental Services Unit extensively sanitized all equipment and furnishings. The ER was reopened at about 7 a.m., and Ramirez was released to the Coroner at 10 a.m.

Affected ER personnel experienced ongoing symptoms long after the incident, and more details are given later in this paper. Subsequent investigations of the hospital's

physical plant by Cal-OSHA, the Riverside Department of Public Works, California Department of Health Services, and an independent engineering firm could not identify any potential sources that might have contributed to the event. These included studies of the hospital ventilation and plumbing/drainage systems, as well as available medications and cleaning supplies.

Extraordinary precautions, including the use of airtight suits with external air supplies, were employed for Ramirez' initial autopsy. These efforts and ensuing events have been chronicled in detail by the popular media. The cause of death [1] was cardiac dysrhythmia, brought about by acute kidney failure. In addition, Ramirez had advanced cervical carcinoma that had spread to the lymph system and had perhaps also produced ureter blockage. Toxicology performed by the Coroner reported standard chemistry panels and the presence of lidocaine, acetaminophen, codeine, and morphine. Ramirez' blood was analyzed for common organic solvents and metabolites, carbamate pesticides, and numerous organophosphate pesticides. In addition, air samples from the scene were analyzed for a number of volatile compounds, such as ammonia, phosgene, HCN, and H<sub>2</sub>S. Only acetone, in Ramirez' system at concentrations of tens of mg/L, was reported to be elevated. The conclusion was that there were no indications of toxic, volatile species or hazardous vapors associated with specimens of Ramirez' tissues and body fluids, or with the air samples.

Autopsy samples were also sent to other laboratories for analytical investigation. For example, the Forensic Science Centre (FSC) at Livermore National Laboratory received specimens of heart, bile, liver, brain, blood, lung, and kidney. Detailed elemental analysis of all samples was performed, and organic analyses of headspace and fluid components of the blood and bile were accomplished by computer-guided gas chromatography/mass spectrometry (GC-MS). In April 1994, the results of these FSC analyses, along with those of other laboratories, were presented at an analysts' meeting convened by the Riverside Coroner.

At another laboratory, an early candidate for a causative agent in this incident was an organophosphate insecticide; however, further analysis eventually rejected this possibility. It was known that Ramirez had started an anti-nausea prescription, Compazine, a couple of days before the incident, and that a number of medications had been administered in the ER. Despite inconsistent statements in the accumulated body of literature, Ramirez had apparently not started radiation therapy or chemotherapy for her cervical cancer. Before the present work, the most recent speculation in the incident encompassed a very minor, mysterious, and as-yet unconfirmed nitrogen-containing compound observed in GC-MS data at the FSC as well as at another laboratory.

To date, a reasonable chemical explanation for the events accompanying the death of Gloria Ramirez has not developed: a plausible solution based on existing analytical data was not straightforward. The potential scenario discussed in this paper postulates an alternative explanation, which does not, however, incorporate any of the above-mentioned species or considerations.

Because of the lack of a credible resolution of this incident, Riverside County requested an investigation by the State of California Department of Health Services. The absence of laboratory and physical results indicating a specific organic cause, as well as some statistical analysis, led the Department of Health Services to issue a report

proposing an outbreak of mass sociogenic illness (mass hysteria) as the most probable explanation [2]. Reaction to this interpretation was not unanimously favorable [3].

In September 1994, a chronological listing and photocopied information on the Riverside incident was sent to the FSC. This file contained copies of numerous press clippings, staff observations, analytical reports, toxicity data, legal claims, and other such materials. It was the receipt of these documents that stimulated an in-depth analysis of the mystery, and led to the proposed scenario discussed in this paper. In particular, copies of the Coroner's Report [1] and Cal-OSHA's accident investigation [4] were especially useful.

In the present analysis, the ER staff observations were taken as reasonably accurate and valid, despite the trying circumstances under which they worked, with a somewhat lesser acceptance of the notion of mass hysteria. The staff were, after all, trained and experienced personnel in health-care emergencies. The Riverside ER admits many patients daily, with a broad range of symptoms and in a vast multiplicity of health and disease states. ER personnel are exposed daily to a wide range of human conditions, and their observations as expert witnesses were important in the development of the present scenario.

## 2. Proposed chemical scenario

What follows is a novel possibility for the events associated with Ramirez' death. We emphasize that this proposed explanation is not an unequivocal proof, and that the exact physiologic and environmental conditions present in the Riverside ER may be impossible to duplicate for a definite confirmation of the scenario. In typical forensic fashion, a best attempt at correlating observations and data with known physical and biologic parameters is what is attempted here.

The present theory is based upon the development of a reaction sequence to explain the reported toxicities, and it is dependent upon a progression of chemical reactions occurring at first in vivo, and then in vitro. Each of these sequential steps is discussed in detail below.

### 2.1. Step 1. Ramirez had accumulated an elevated concentration of DMSO

It is reasonable to surmise that Ramirez had a quantity of a potent solvent, dimethyl sulfoxide [DMSO,  $(\text{CH}_3)_2\text{SO}$ ] in her system, and that it was in her blood when the ambulance arrived. The principal support for this statement is that GC-MS analyses of blood and bile samples (see Fig. 1) gave conclusive evidence for the presence of the metabolic oxidation product of DMSO, dimethyl sulfone [ $\text{DMSO}_2$ ,  $(\text{CH}_3)_2\text{SO}_2$ ]. In addition, one of the ER staff reported 'a fruity, garlic odor approximately 12 to 18 inches from the patient's mouth' during the incident ([4], p.7). The presence of a garlic-like odor on the breath of someone who has ingested DMSO is characteristic of exposure to this chemical [5].

DMSO is an unusual compound. It is a colorless, oily, organic liquid at room temperature, with little odor unless metabolized. It is very polar, strongly hygroscopic,

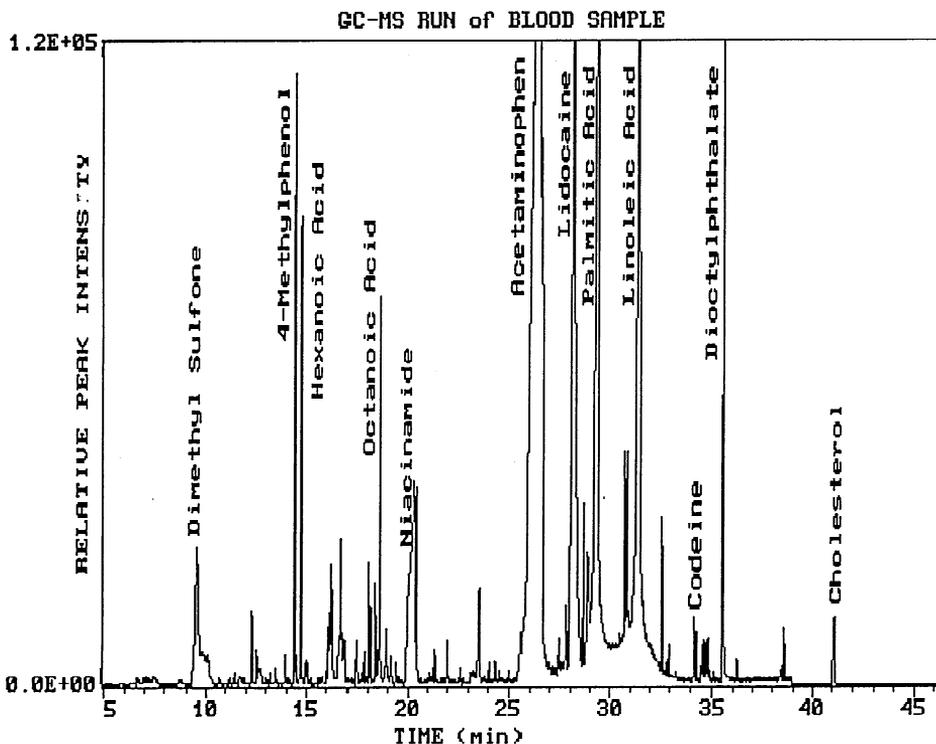


Fig. 1. Total-ion GC-MS chromatogram of Gloria Ramirez' blood sample. Analysis conditions: Hewlett-Packard 5890 GC with 5988 quadrupole MS; 30-meter Alltech SE-30, methylsilicone capillary column with 0.25 mm I.D. and 0.25  $\mu\text{m}$  film thickness; splitless injection mode with 1 min residence time at 250°C; thermal gradient program: 5 min holding time at 30°, followed by 8°/min ramp to 320° and hold for 5 min; electron-impact ionization at 70 eV; data acquisition began at 5 min after injection.

and miscible with aqueous solution in any proportion [6,7]. DMSO is derived from wood pulp and is capable of dissolving many organic and inorganic species. Its main industrial uses are as an aprotic solvent, as a reaction medium and reactant for chemical syntheses, and as an antifreeze [8]. DMSO is also used for cellular preservation, and exhibits cryo- and radiation-protection properties [9]. Perhaps the most notable property of DMSO, however, is its ability to easily penetrate organic membranes, including the skin, without damaging the integrity of those membranes [10]. Indeed, DMSO can traverse the dermal barrier quickly and in high concentration, carrying other dissolved species with it, without causing any permanent tissue damage.

Why might Ramirez have had an elevated concentration of DMSO in her system? Reasonable answers to this question are only speculative in nature. One possibility, which was referenced in the OSHA accident investigation [4], is that Ramirez had used the recreational drug phencyclidine (PCP) and had absorbed it through her skin with a DMSO-based carrier cream. A preliminary description attributed to the Riverside Coroner's Office ([4], p. 10) stated that Ramirez had indications at autopsy consistent

with PCP use. We note that the OSHA report later stated that analyses did not support the implications of PCP and DMSO use ([4], p. 17). The identities and sensitivities of these analyses were not disclosed. However, no evidence for PCP was detected in any of the specimens analyzed by the FSC.

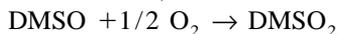
There are any number of other credible reasons why Ramirez might have used DMSO. Although only limitedly prescriptive within the U.S. (primarily for interstitial cystitis), it has long been used as an unofficial home remedy, and it is readily available domestically for veterinary applications. There is also a scientific literature of DMSO portraying it as something of a wonder drug. For example, it has been found to exhibit pronounced analgesic effects in the relief of intractable pain of diverse origin [11], and it is also commonly used as an anti-inflammatory agent and analgesic for the alleviation of pain in muscles and joints [12]. DMSO has also been established as an agent for significant antianxiety, antipsychotic, and psycho-stimulant effects, and has thereby found use as a sedative and tranquilizer [7]. DMSO has been utilized as an antibacterial agent in cancer patients [13], and has also been used in therapy of cervical cancer [14]. Indeed, DMSO has even found use as a vehicle for antiperspirant [15]. There are thus many plausible reasons, other than illegal drug use, that could account for the presence of DMSO in Ramirez' system.

It is uncertain whether the DMSO might have arisen from an acute application just prior to the incident, or whether it might have been accumulating for some time. The normal routes of DMSO elimination from the body are through respiration and urinary excretion [7,16,17]. A small percentage (~3%) of ingested DMSO is reduced to dimethyl sulfide [(CH<sub>3</sub>)<sub>2</sub>S] and is eliminated mainly through the lungs and skin, giving rise to the 'garlic-like' odor. The principal metabolite of DMSO is DMSO<sub>2</sub>, which is produced in the liver by microsomal oxidation in the presence of NADPH<sub>2</sub> and O<sub>2</sub>. The DMSO<sub>2</sub> is then excreted primarily through the kidneys.

The Coroner's Report indicated that Ramirez had obstructive uropathy. This condition may have hindered urinary excretion and resulted in an accumulation of DMSO in her system. Moreover, since Ramirez had been suffering from severe nausea and had been vomiting for several days, she was likely quite dehydrated, with minimal voiding and DMSO elimination, regardless of ureter status. The exact mechanism for the presence of DMSO in Ramirez' body is relatively immaterial; the notable point is that it was most likely present when she was picked up by the ambulance on the night of the incident.

## 2.2. Step 2. The DMSO was oxidized to DMSO<sub>2</sub> in vivo

This next step in the proposed incident scenario is also reasonably certain. As discussed above, the oxidation reaction

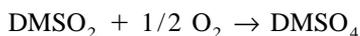


is the principal metabolic pathway. Moreover, the presence of DMSO<sub>2</sub> at elevated levels was conclusively identified by GC-MS analyses of autopsy samples (Fig. 1). It is reasonable to presume that the oxygen administered to Ramirez, in both the ambulance and the ER, drove this reaction strongly to the right. In fact, DMSO was not similarly detected in these same samples (limit of detection ~ ng); a legitimate inference from this information, therefore, is that the above reaction went essentially to completion.

DMSO<sub>2</sub> is a white crystal at room temperature, and it is freely soluble in aqueous solution [8]. The solubility of DMSO<sub>2</sub> will be discussed later in this paper.

### 2.3. Step 3. The DMSO<sub>2</sub> was further converted to DMSO<sub>4</sub>

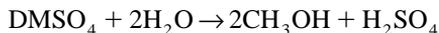
It is proposed that, under the conditions of this incident, the oxidation reaction of DMSO continued onward from DMSO<sub>2</sub> to ultimately produce dimethyl sulfate [DMSO<sub>4</sub>, (CH<sub>3</sub>O)<sub>2</sub>SO<sub>2</sub>] in the overall reaction:



As far we know, the direct conversion of DMSO<sub>2</sub> → DMSO<sub>4</sub> has not been specifically observed before, and it is the potential key to the mystery of the incident. DMSO<sub>4</sub> can be produced synthetically by the reaction of methanol with sulfuric acid. However, under the manually-assisted oxygenation and pathologic blood chemistry accompanying Ramirez' death, it is conceivable that biochemical reactions of enzymes and/or free radicals could have catalyzed the oxidative conversion of DMSO<sub>2</sub> to DMSO<sub>4</sub>.

A likely intermediate in this potential scheme might be the sulfate anion (SO<sub>4</sub><sup>=</sup>), and there is some experimental evidence that DMSO can be metabolically oxidized completely to sulfate. For example, bacteria are known to oxidize DMSO through DMSO<sub>2</sub> to sulfate [10], and, under normal oxygen and metabolic conditions, a small quantity of sulfate has been measured from the oxidation of DMSO in animal studies [16,18]. With sulfate as a reaction intermediate, DMSO<sub>2</sub> could also act as a methyl-group donor [10], and a chemical chain reaction to produce DMSO<sub>4</sub> would be possible (mechanistic considerations will be expanded upon later in this paper). Further, DMSO is known to safeguard biologic systems from the deleterious effects of free radicals by virtue of its ability to be oxidized by the free radicals [19]; there is experimental evidence for the enzyme-oxidation of DMSO [20]; and DMSO has been observed to both inhibit and stimulate enzyme-catalyzed reactions [20].

DMSO<sub>4</sub> is a colorless, oily liquid at room temperature [8]. It has a limited solubility in aqueous solution, 28 mg/ml at 18°C (64°F), and rapidly hydrolyzes at temperatures above that to methanol and sulfate:



An open-literature reference indicates that DMSO<sub>4</sub> has been considered useful as war gas [8], and it can also be found listed in the classified literature as a chemical warfare agent [21]. The Merck Index [8] describes DMSO<sub>4</sub> as extremely hazardous, with no early-warning characteristics. DMSO<sub>4</sub> vapor can be inhaled or, like DMSO, absorbed directly through the skin. Symptoms may be delayed to the point of permitting unnoticed exposure to lethal concentrations, and serious poisoning can occur by the transcutaneous route. DMSO<sub>4</sub> vapors, following a relatively asymptomatic latent period, can induce severe reactions and death in exposed individuals.

The toxicity of airborne DMSO<sub>4</sub> has been measured in rats [22]: the maximum time that saturated vapor could be inhaled without resultant death was 2 min, and the

inhalation of 30 ppm for 4 h caused mortality in 5 of 6 rats within 14 days. In another reference [21], the lethal concentration for humans is listed as 500 mg/m<sup>3</sup> for 10 min.

An instructive exercise was to compare the known physiologic effects of DMSO<sub>4</sub> with those reported by the afflicted victims in the Riverside ER. The information sources for the ER symptoms were the quotations, notes, documents, and legal claims found in the file sent to the FSC. Several references describing the aftermath of DMSO<sub>4</sub> exposure were readily available at LLNL [8,21,23–25]. Table 1 is a comparison of the toxic effects and observations reported in the Riverside incident with those known to be induced by DMSO<sub>4</sub>. This table is divided into three sections, differentiating the immediate symptoms experienced in the ER, the symptoms that were prolonged for some time after the incident, and those additionally experienced by Dr. Gorchynski, the individual reported to be the most severely affected of the victims. The descriptors and verbiage used in the DMSO<sub>4</sub> column are taken directly from the indicated references.

The one-to-one correspondence between the two columns is striking. Of the 20 symptoms reported by the ER victims, only one (nausea and vomiting) could not be

Table 1  
Physiologic effects of Riverside ER incident vs DMSO<sub>4</sub>

Riverside ER Victims	DMSO <sub>4</sub>
<i>Immediate symptoms</i>	
Ammonia-like odor	Onion odor [21]
Dizziness	Dizziness (a 1st symptom) [23]
Fainting	Prostration [8]
Respiratory irritation	Severe inflammation and necrosis of respiratory tract [8]; pulmonary edema [21,23]
Suffocation	Severe/fatal pulmonary damage [8]
Reduced heart rate	Bradycardia [24]
Nausea and vomiting	–
Flushing and burning skin	Blistering of skin [8,21]; vesicant [21]
Headache (frontal, bilateral)	Headache (a 1st symptom) [23]
Lacrimation	Burning eyes (a 1st symptom) [23]
<i>Prolonged symptoms</i>	
Uncontrolled tremors; violent muscle spasms	Convulsions [21]
Respiratory failure (apnea)	Severe/fatal pulmonary damage [8]; paralysis [21]
Unconsciousness	Drowsiness [24]; coma [21]
Concentration loss; severe memory lapses	Cerebral edema [24]
Shortness of breath	Respiratory dysfunction [24]
Restrictive lung disease	Severe/fatal pulmonary damage [8]; pulmonary edema [21,23]
<i>Gorchynski additional symptoms</i>	
Massive osteonecrosis (knees)	(Delayed heart damage [8])
Hepatitis	Delayed liver damage [8]; General injury of internal organs [25]
Pancreatitis	General injury of internal organs [25]
Recurring nightmares	Delirium [21]
Flashbacks	Delirium [21]
–	Delayed kidney damage [8]

found in the cited references on  $\text{DMSO}_4$  effects. Conversely, of the symptoms attributed to  $\text{DMSO}_4$  exposure, only two (burning eyes and delayed kidney damage) were not initially found in the reported, first-hand accounts and legal claims associated with the Riverside incident. As will be discussed later, however, now only delayed kidney damage is not currently correlated with the incident.

One table entry (delayed heart damage aligned with Gorchynski's osteonecrosis) is enclosed in parentheses to indicate that this potential correlation is somewhat more oblique than the others. The idea here was that any induced heart damage might adversely impact blood circulation, and that a potential preexisting condition (such as surfer's knots) might be more at risk for serious consequences. (Gorchynski is reputed to have been an avid surfer.)

A similar exercise was performed to compare the ER victim symptoms with sewer gas (taken to be  $\text{H}_2\text{S}$ ). As might be expected with another respiratory toxin, there was also some degree of overlap between  $\text{H}_2\text{S}$  and the Riverside symptoms, particularly in the immediate effects. However, the correspondence with consequences arising from the inhalation of  $\text{H}_2\text{S}$  was decidedly inferior to that from exposure to  $\text{DMSO}_4$ , and  $\text{H}_2\text{S}$  would not account for any of Gorchynski's additional symptoms.

#### 2.4. Toxicology and semiquantitative speculation

What concentrations of these various  $\text{DMSO}_x$  compounds are both necessary and plausible for their potential participation in this incident? The parent compound, DMSO, is soluble in aqueous solution in any proportion [6,7]. It consequently has a very high solubility in human blood. However, DMSO exhibits very low toxicity, the single-dose  $\text{LD}_{50}$  in mice and rats for dermal administration being estimated at 40–50 g/kg [26]. The optimum concentration of DMSO for dermal transport is 90% (by volume) in water [10], and treatment periods over several months, to the extent of 60 ml/day, have been well tolerated in patient studies [7]. It is thus conceivable that Ramirez could have accumulated an appreciable concentration of DMSO in her blood, perhaps tenths of a gram per ml, so that the potential availability of the parent compound in her system would not be a limiting factor in this overall chemical scenario.

The first oxidation product,  $\text{DMSO}_2$ , is reported to be freely soluble in water [8]. To get a better estimate of the meaning of this statement with respect to the Riverside incident, we performed a measurement of the solubility of  $\text{DMSO}_2$  at physiologic temperature ( $37^\circ\text{C}$ ) in a simulated, transparent blood medium (Krebs Improved Ringer Solution). The semiquantitative result was approximately 0.5 g/ml.

The definition of the Standard Adult Woman [27] includes a value for the total blood volume of the 58 kg standard. Scaling that volume to Ramirez' estimated body weight (~110 lb: [4], p. 12) and multiplying by 0.5 g/ml gives a computed result of 1.7 kg. While such a large body burden of  $\text{DMSO}_2$  is not credible, it will soon be shown that a quantity of this magnitude is unnecessary for the incident. This calculated, kg-quantity of  $\text{DMSO}_2$  is merely an estimate of a solubility limit imposed on the problem by fundamental physical chemistry, and indicates that a large amount of this compound can also be potentially dissolved in human blood.

As discussed earlier, the ultimately oxidized reaction product,  $\text{DMSO}_4$ , is extremely

toxic, and human lethality has been quoted as 500 mg/m<sup>3</sup> for 10 min [21]. This exposure can be conservatively integrated by using the lung ventilation rate of the Standard Adult Man [27]. Under light activity and the standard ventilation of 20 l/min, the fatal dosage of DMSO<sub>4</sub> would be a total of approximately 0.1 g. Since none of the ER staff died as a result of this incident, all of the individual exposures would therefore have been presumably below the 100-mg level, conceivably in a range of tens or hundreds of µg to perhaps a mg or tens of mg. If a total release of tenths of a gram of DMSO<sub>4</sub> is assumed for this incident (and diluted upon dispersal into µg-mg single exposures), it would require only tenths of a gram of the precursor compounds DMSO and DMSO<sub>2</sub> under efficient synthesis conditions. As shown above, this and much larger quantities of both precursors are well within the range of possibility for human blood.

### 3. Scenario Integration

The following is a developed scenario for the overall incident based upon the chemical scheme proposed above. It is again emphasized that it is only a technically grounded analysis that may have some potential validity, but which could also prove to be deficient upon future disclosures.

When Gloria Ramirez was picked up by the ambulance, she had accumulated an unknown concentration of DMSO in her blood. As she was continuously administered oxygen in the ambulance and the ER, the oxidation of DMSO to DMSO<sub>2</sub> was accelerated. A possible reason that the ambulance personnel were unaffected, despite the spillage of a small amount of blood in close confinement en route to the hospital, was that this contact with Ramirez' blood occurred early in the incident, before appreciable oxygenation had taken place. It is also possible that the temperature in the ambulance was above the DMSO<sub>4</sub> hydrolysis threshold (see below).

At the time of treatment in the ER, an elevated concentration of DMSO<sub>2</sub> had been formed in the blood, and was being maintained in her system at a nominal temperature of ~37°C. Any DMSO<sub>4</sub> that might have been produced in vivo would have been immediately hydrolyzed to methanol and sulfate. When her blood was drawn in the ER, the temperature of the medium fell from ~37° to ambient (18° or lower?), and the solubility product of DMSO<sub>2</sub> in blood was exceeded. Ramirez' withdrawn blood became supersaturated, and white crystals of DMSO<sub>2</sub> precipitated in the syringe.

As a collateral effort to the measurement of DMSO<sub>2</sub> solubility in Ringer solution, this precipitation effect was dramatically demonstrated. Fig. 2 shows the experimental apparatus. A large beaker served as a water bath, and it was maintained at 37°C by a combination hot plate/magnetic stirrer. Inside the beaker was an equilibrated, 40-ml glass centrifuge cone containing 10 ml of Ringer solution. Although difficult to see in this photograph, the solution had been loaded to about 0.5 g/ml with DMSO<sub>2</sub> and was slightly cloudy, indicating the approximate onset of precipitation. This same solution was then allowed to cool to room temperature (22°C), with the result shown in Fig. 3.

The syringe containing Ramirez' blood was now a saturated solution of DMSO<sub>2</sub>, with excess DMSO<sub>2</sub> also precipitated. The medium was also highly oxygenated and contained a suite of enzymes and/or free radicals. Reaction of some DMSO<sub>2</sub> to DMSO<sub>4</sub>

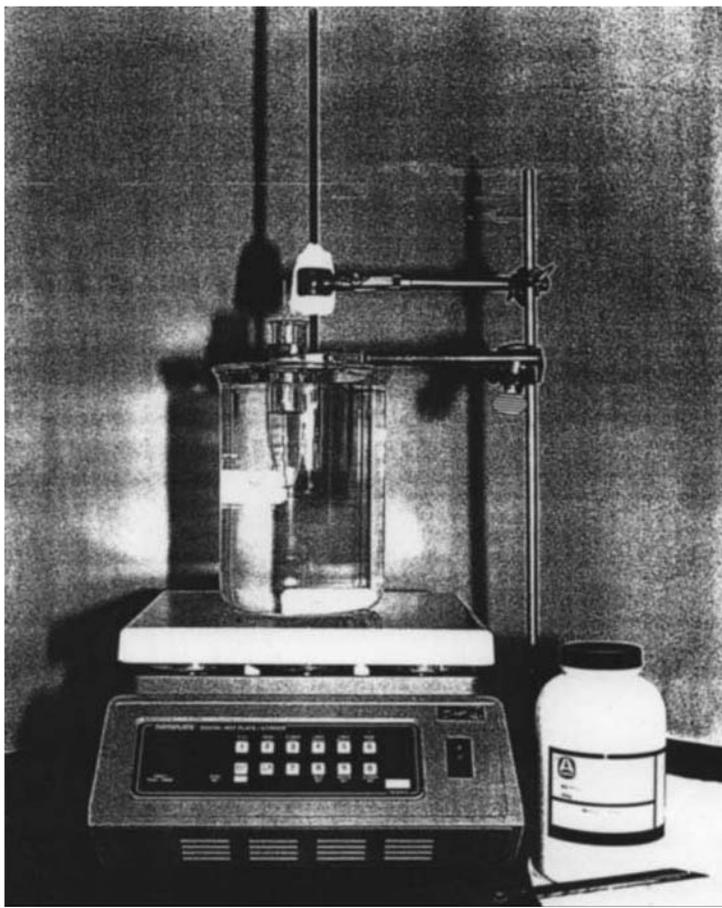


Fig. 2. Experimental apparatus used for the measurement of  $\text{DMSO}_2$  solubility in Ringer solution at  $37^\circ\text{C}$ . The solution in the central cone is at the onset of precipitation.

occurred. The  $\text{DMSO}_4$  did not undergo effective hydrolysis at the reduced temperature, and was soluble only to an approximate extent on the order of  $\sim 30$  mg/ml in the medium. The remainder survived intact and divided from the solution as a colorless, separate phase. Some fraction then volatilized into the vapor space to assail the ER personnel.

Crystals were not subsequently found in the withdrawn blood sample because reaction of  $\text{DMSO}_2$  to  $\text{DMSO}_4$  (and perhaps to other species as well) had taken place. As indicated earlier in this paper, a large quantity of  $\text{DMSO}_4$  is not required to elicit the toxicity reported in the incident ( $\mu\text{g}$ -mg), and the compound is described as 'nonpersistent under field conditions' [21]. It is therefore not surprising that the only enduring evidence of the chemical attack might be the symptoms of the victims.

Ramirez' body was described by some staff as having an oily, shimmering sheen

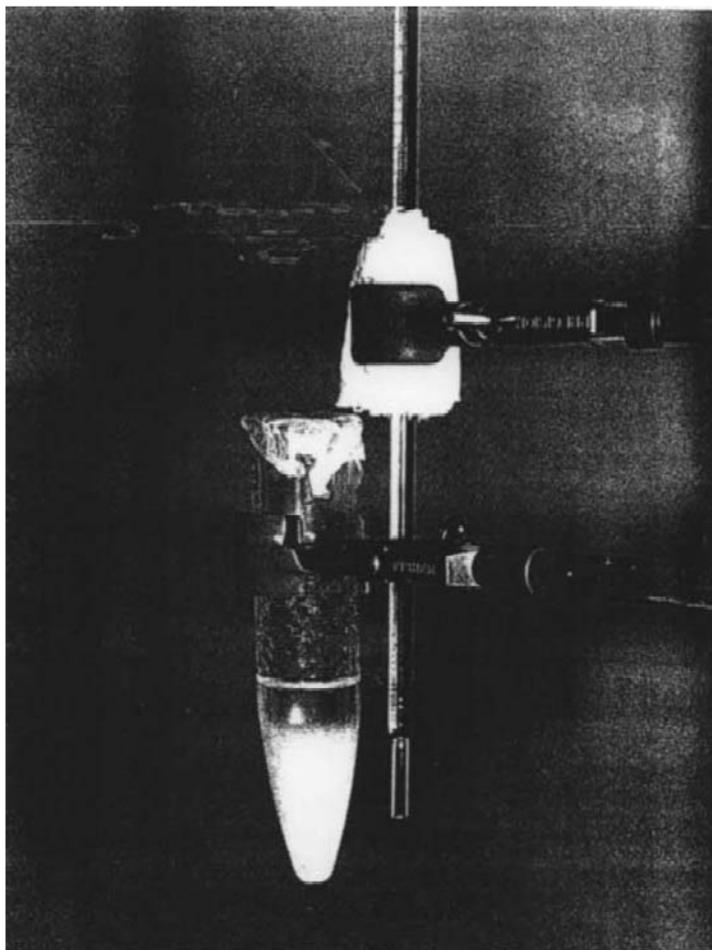


Fig. 3. The solution of Fig. 2 upon cooling to 22°C.

when she was admitted to the ER. As a final speculation on the incident, it is noted that the topical application of DMSO can cause dermatitis, although it is usually described as irritation with redness [8]. However, a double-blind study of DMSO side effects concluded that ‘the severity or absence of odor and skin irritation could not be predicted on a basis of age, color of hair, geographic ancestry, or racial origin. This was an individual characteristic based upon tolerance and metabolic factors not yet understood’ [28].

#### **4. Scenario History, Feedback, and Further Work**

The above theory was our original, proposed explanation for the Riverside incident,

and it was sent to the Riverside Coroner in late October 1994 as an ‘In Strict Confidence, Preliminary Draft’ report. It was to undergo further peer review by eminent consultants that the Coroner had retained specifically for the incident. However, because the scenario apparently had reasonable credibility upon initial review, it was divulged to the public immediately and over the protest of the LLNL General Counsel. This release was done in the name of good-faith, full disclosure to the ER victims, several of whom were still suffering symptoms in the aftermath of the incident. Presumably, their continuing health care might benefit from some consideration of the postulated chemical scenario. Since then, we have received, or have been informed of, specific comments on the incident analysis from the scientific community. While this feedback has not yet been so persuasive as to seriously impact the developed proposal, some major points of contention are discussed here.

#### 4.1. Caveats

It was argued, by proponents of DMSO for the health industry, that the presence of  $\text{DMSO}_2$  in Ramirez’ system was not unequivocal proof that she had ingested DMSO: she could have consumed  $\text{DMSO}_2$  directly. That is possibly true. The only source of DMSO implication was the OSHA report [4], and the evidence was anecdotal (garlic smell on Ramirez’ breath, body sheen, etc.). Moreover, it is also within the realm of possibility that her pathology might have somehow metabolized  $\text{DMSO}_2$  from S-containing amino acids. However, in light of the historic (e.g., [29]) and continuing [30,31] popular reputation of DMSO in American society, we consider the latter two possibilities to reasonably be much lower-probability considerations. Nevertheless, they cannot be absolutely discounted.

The only impact that non-DMSO inputs of  $\text{DMSO}_2$  would have on the postulated scenario would be the consideration of the ambulance aspect of the incident. Enhanced oxygenation would then be unnecessary to accelerate  $\text{DMSO} \rightarrow \text{DMSO}_2$ , although it might still be required for conversion of  $\text{DMSO}_2 \rightarrow \text{DMSO}_4$  in the ER. Whether or not Ramirez truly ingested DMSO prior to this incident is actually somewhat peripheral to concerns about DMSO safety, however, because it is the  $\text{DMSO}_2 \rightarrow \text{DMSO}_4$  transformation that is pivotal. A straightforward metabolic evolution of DMSO to  $\text{DMSO}_2$  is conventional, well-documented, and not ordinarily disputed.

#### 4.2. Potential $\text{DMSO}_2 \rightarrow \text{DMSO}_4$ mechanisms

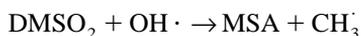
Because Ramirez’ biochemical reaction properties were incompletely known, we had purposely avoided any detailed speculation on chemical mechanisms for the proposed  $\text{DMSO}_2 \rightarrow \text{DMSO}_4$  reaction until this time. However, recent criticism by organic chemists has erroneously assumed that this reaction required the insertion of oxygen atoms into C-S bonds. That assertion is not true and would indeed be a difficult synthetic proposition if necessary. Nevertheless, there is, in fact, chemical precedent for just that mechanism. In the reaction of  $\text{CH}_3\text{SH}$  with oxygen radicals, generated by the photolysis of ozone,  $\text{CH}_3\text{OSH}$  was a reported product [32].

We present two possible reaction mechanisms that might accomplish the  $\text{DMSO}_2 \rightarrow$

DMSO<sub>4</sub> conversion without O-atom insertion into existing bonds; more may be possible. These mechanistic details are necessarily speculative for the incident under consideration, but they have some precedence in previously-reported chemical studies.

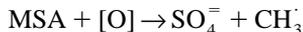
Both mechanisms rely on the existence of extraordinary oxidizing conditions. However, it is well known that disease states, the dying process, and super-oxygenation generate and elevate elemental oxygen, OH·, O<sub>2</sub><sup>-</sup>, and other reactive species in biologic systems [33–37].

1. The first hypothetical mechanism would transform a given molecule of DMSO<sub>2</sub>, through various intermediate species, to a resultant molecule of DMSO<sub>4</sub>, perhaps with the assistance of attendant enzymes. The initial step would be the reaction of DMSO<sub>2</sub> with OH· to form methanesulfonic acid [MSA, (CH<sub>3</sub>)SO<sub>2</sub>OH]:



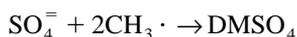
The very similar reaction, DMSO + OH· → methanesulfinic acid as a primary product has been observed [38,39], and, although no detailed product analysis was conducted, an experimental study of the oxidation kinetics of DMSO<sub>2</sub> with OH· has been reported [40]. Moreover, it is well known that both DMSO and DMSO<sub>2</sub> can be produced under oxidizing conditions from dimethyl sulfide [DMS, (CH<sub>3</sub>)<sub>2</sub>S] [41], and that MSA has been measured as another DMS oxidation product upon reaction with OH· [42,43].

The second step in this mechanism would have MSA further oxidized to the sulfate anion:



Sulfate has been identified as an oxidation product of MSA in both bacterial action [44] and in reaction with OH· [40,45]. Additionally, sulfate was measured as one of the oxidation products of DMS in an environmental study [46].

This sequence of reactions, from DMSO<sub>2</sub> to sulfate, has been suggested before as potential metabolic products of DMSO [10]. Finally, the mechanism is completed by the methylation of the sulfate ion:

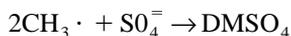


From the observed evolution of CH<sub>4</sub>↑ in DMSO experiments [47,48], the conclusion that DMSO can serve as a methyl-group donor is reasonable. From the standpoint of conventional organic chemistry, DMSO<sub>2</sub>, by virtue of its additional electron-withdrawing S=O bond, should be an even better methyl-group donor than DMSO.

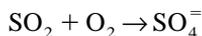
2. The second potential mechanism is a variant of the first, but would utilize naturally-occurring sulfate in the body as a seed reactant. In that way, the function of the DMSO<sub>2</sub> is only as a methyl donor. Complete stepwise demethylation of DMSO<sub>2</sub> might provide the following effective species in an overall reaction:



The methyl groups would then be free to potentially react with existing sulfate to form DMSO<sub>4</sub>, as in the last step of the first mechanism:



Any resultant  $\text{SO}_2$ , produced in the strongly oxidizing medium, would likely be ultimately oxidized to sulfate:



An intriguing aspect of the present mechanism is that, for each sulfate anion consumed to produce  $\text{DMSO}_4$ , one is replenished by the oxidation of  $\text{SO}_2$ . The availability of only a single sulfate ion would therefore be adequate to initiate a chemical chain reaction, with the limiting reactant being the (potentially copious) quantity of  $\text{DMSO}_2$  in Ramirez' system.

#### 4.3. Sulfate measurement

If  $\text{DMSO}_4$  was hypothetically formed in vivo as well as in vitro, hydrolysis to sulfate would have been the likely reaction pathway. Approximately 1 g of Ramirez' blood sample was extracted twice with ( $\sim 60^\circ\text{C}$ ) water, and quantitative analysis for inorganic sulfate was effected by ion chromatography (IC) [49]. The result was 590  $\mu\text{g/g}$  (620  $\mu\text{g/ml}$ ). The normal clinical values of inorganic sulfate in blood have been listed as 8–20  $\mu\text{g/ml}$  [50] and 29–35  $\mu\text{g/ml}$  [51]. Taking the low and high values of these literature ranges implies that Ramirez' blood was elevated in sulfate by a factor of  $\sim 20$ –80. While this is an interesting result, it is not definitive proof of  $\text{DMSO}_4$  formation. As discussed in the mechanistic considerations above, it appears possible to also generate excess sulfate from  $\text{DMSO}_2$  oxidation.

#### 4.4. Recent information

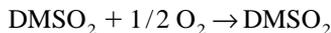
In the preliminary version of this paper, Table 1 had no correlation between the burning eyes associated with  $\text{DMSO}_4$  exposure and the reported ER symptoms. Critics have suggested that, as a first symptom of  $\text{DMSO}_4$  attack, the absence of eye involvement in the Riverside incident was a critical shortcoming. Our only source of incident information at that time was the literature file sent by Welch, and reported tearing by the victims was not found in it. We speculated that perhaps it was so minor in comparison to more serious consequences that it was overlooked in the popular accounts of the incident. Another possibility was that lachrymal response was dependent on direct contact with the eyes, and that perhaps transcutaneous ingestion of  $\mu\text{g}$ - $\text{mg}$  quantities of  $\text{DMSO}_4$  was possible without lacrimation.

Since then, we have viewed a videotaped seminar on the Riverside incident by Drs. Gorchynski and Brett Nelson before a medical audience. It was presented before the release of our preliminary report by the Coroner. In it, a viewgraph was shown that summarized the major symptoms exhibited by the four most seriously affected ER victims. Lacrimation was listed for all four. Consequently, Table 1 has been updated to reflect this more recent information.

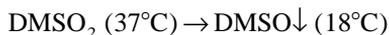
## 5. Summary and Conclusions

A potential chemical explanation for the events associated with the death of Gloria Ramirez has been presented. In chemical shorthand, it can be summarized as:

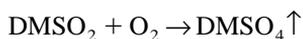
Metabolism:



Precipitation:



Toxic Release:



The final, volatile product is extremely poisonous.

The proposed scenario has several positive points. Its foundation is merely the extension of a reaction modality (oxidation) that is known to have been operational in Ramirez and would logically be heightened by the circumstances of her situation. Further, the chemical and toxic properties of the postulated chemical species are just right. That is, the DMSO and DMSO<sub>2</sub> precursors are very soluble in aqueous media, have negligible toxicity, and are readily obtainable. Conversely, DMSO<sub>4</sub> is quite toxic in very small quantities, has a limited aqueous solubility, and possesses adequate volatility.

In our estimation, the correspondence between DMSO<sub>4</sub> effects and the symptomatics of the Riverside ER incident, summarized by Table 1, is quite good.

The weakest point of the scenario is probably the lack of an established precedent for DMSO<sub>2</sub> → DMSO<sub>4</sub>. However, reasonable potential mechanisms for that transformation have been presented. Moreover, if everything about the Riverside incident were standard fare, it would presumably have been less of an enigma.

From the (incomplete) information and details of the incident that are presently known to us, the developed scenario appears to provide an excellent match for potentially answering many of the questions, and resolving much of the mystery, surrounding the event. However, additional studies would be necessary to substantiate (if, in fact, it is possible) the likely validity of the chemical sequence. The proposed scenario would undoubtedly benefit from modification and refinement that would only be possible upon the disclosure of further details of the incident by the ER staff. For example, what was the type and design of the syringe, and what were the specifics of the venipuncture procedure? Is it credible that fumes could have escaped from this syringe, at that time, under the existing conditions?

The basic chemical scenario could potentially accommodate, and likely be strengthened by, any loss of body fluid that Ramirez experienced in the ER. Was any blood spilled or exposed to the environment during the second IV or in aliquoting the blood from the syringe into three vacutainer tubes? In her videotaped seminar, Gorchynski indicated that Ramirez vomited after intubation. A revision of the proposed scenario to more closely match the details of the actual experience would only be possible with reasonable feedback from eyewitness accounts.

We have already tried, through the Riverside Coroner's Office, to get additional, pertinent information from Riverside General Hospital. For example, could any of the staff recollect or make a rough estimate of the likely temperature in the ER during the night of the incident? Was it, like many emergency facilities, on the cool side and probably <65°F, or was it likely warmer? Unfortunately, because of the adversarial evolution of this case and the current legal ramifications, an answer was not forthcoming.

We thus still have some unanswered questions that we will apparently be unable to address. Final conclusions and judgment of the proposed scenario will therefore likely depend upon further scrutiny by expert analysts in various fields of medicine, physiology, toxicology, pharmacology, and forensic science.

If the candidate reaction sequence was in operation during the Riverside episode, it may have been unique to Ramirez' specific pathology. However, it is also conceivable that a confluence of elevated DMSO concentration, oxygenation, high voltage, and cooler hospital facilities might be a condition for more widespread concern. If so, health-care providers should be made aware of the possible consequences of such reactions and exercise appropriate precautions.

## **Acknowledgments**

We are grateful to Dr. Jim Meeker of the Institute of Forensic Sciences for initial technical discussions and helpful comments on the proposed chemical scenario. His expertise in the areas of toxicology and pharmacology was invaluable, but he is in no way responsible for the contents of this paper. That is the sole burden of the authors.

Thanks are due to Terry Fickies of the California Department of Justice and to Dan Cupido of the Riverside Coroner's Office for requesting the assistance of Livermore's Forensic Science Center in the investigation of this incident. Enlightening conversations on emergency room experiences and procedures with a local ER nurse are gratefully acknowledged, as is the help of Rick Russo, Nora Butler-Briant, Colleen Amick, and Craig Savoye at LLNL and LBL. Verbal commentaries on the preliminary report by Drs. Stan Jacob (Oregon Health Sciences Univ.), Jeff Burgess (Washington Poison Center), and Chuck Kelly (Massachusetts College of Pharmacy) were very helpful. We are most appreciative of technical comments and the administrative assistance provided by Dr. Alan Mode of LLNL. Finally, the present analysis would have been impossible without the aid of Maureen Welch, who generously sent us her own personal file and auxiliary information on the Riverside incident.

The specific medical information on various individuals described in this paper was obtained from public sources: either media accounts of the incident or from one or more of the listed references. To the knowledge of the authors, this information was accurate and correct. However, we had no access to data that were obtained by patient-physician interactions.

This work was performed under the auspices of the U. S. Department of Energy by Lawrence Livermore National Laboratory under contract W-7405-ENG-48.

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