

EUR/ICP/PCS 0104  
ORIGINAL: ENGLISH

45409 *MR*

**TOXIC OIL SYNDROME AND  
EOSINOPHILIA-MYALGIA  
SYNDROME  
CLINICAL ASPECTS**

**Report on a Workshop**

**Stony Brook, New York  
27-29 October 1992**

1993

EUR/HFA target 22



# CONTENTS

|                               | <i>Page</i> |
|-------------------------------|-------------|
| Introduction                  | 1           |
| Neuromuscular manifestations  | 2           |
| Respiratory manifestations    | 5           |
| Skin manifestations           | 6           |
| Eosinophil involvement        | 8           |
| Neurocognitive dysfunction    | 10          |
| Fibromyalgia                  | 11          |
| Animal models                 | 12          |
| Overall conclusion            | 12          |
| Future action                 | 13          |
| Annex 1: List of participants | 16          |



## Introduction

In May 1981, a foodborne epidemic broke out in Madrid and its environs. The disease, called the toxic oil syndrome (TOS), developed in people who consumed adulterated rapeseed oil sold illegally as edible oil. TOS affected more than 20 000 persons and resulted in several hundred deaths in the first year. While most of those affected lead normal lives, a number remain symptomatic today.<sup>a</sup>

In November 1989, a disease outbreak, called the eosinophilia-myalgia syndrome (EMS), was recognized in the United States. EMS is associated with ingestion of L-tryptophan as a health food supplement. More than 1500 people were affected in the United States, with additional cases in Canada, Germany, Spain and the United Kingdom, among other countries. TOS and EMS resemble each other more than they do any other disease, sharing such common features as severe myalgias, intense eosinophilia and multisystem involvement. Both syndromes also appear to have the potential for similar long-term sequelae.

In May 1991, a WHO Workshop on the Toxic Oil Syndrome and Eosinophilia-myalgia Syndrome: Pursuing Parallels in Pathogenesis was held in Washington, DC, to compare and contrast the clinical, pathological, epidemiological, immunological and toxicological features of these two diseases.<sup>b</sup> Among the recommendations emanating from the workshop was the following: "To standardize the descriptions of the clinical findings of both syndromes, an international team of physicians should be assembled to collaborate in examining the people affected by TOS or EMS".

The first step in putting this recommendation into action was the EMS/TOS Clinicians' Meeting, held in Madrid, 4-6 May, 1992, under the auspices of the former Fondo de Investigación Sanitaria (now the General Directorate of Research, Planning and Training). Fifteen physicians from Spain and ten physicians from the United States examined patients across the spectrum of signs and symptoms that comprise TOS.

---

<sup>a</sup>*Toxic oil syndrome: current knowledge and future perspectives.* Copenhagen, WHO Regional Office for Europe, 1992 (WHO Regional Publications European Series No. 42).

<sup>b</sup>*Toxic oil syndrome and eosinophilia-myalgia syndrome: pursuing parallels in pathogenesis.* Copenhagen, WHO Regional Office for Europe, 1991.

The second step in carrying out the recommendation from the Washington workshop was to enable the international team of physicians to examine EMS patients. Participants would then be able to compare and contrast the two syndromes based on first-hand experience.

Therefore, a two-and-one-half-day workshop was organized by the WHO Regional Office Europe, in collaboration with the Spanish General Directorate of Research, Planning and Training, the US Centers for Disease Control and the Stony Brook Health Sciences Center of the State University of New York at Stony Brook. The workshop was attended by 31 temporary advisers and 6 observers (see Annex for list of participants). Nine patients were examined and four patient histories were presented for comment.

This report concentrates on EMS, summarizing the relevant clinical issues and comparing the clinical picture of this disease to that of TOS. A full report that covers both meetings of the clinical aspects of the two syndromes is being prepared for journal publication.

## Neuromuscular Manifestations

Neuromuscular involvement in EMS is expressed as myopathy, neuropathy, cramps, spasms and involuntary muscle movement. Because most patients with EMS have a combination of these conditions, they can best be grouped under the term neuromyopathies. However, as most patients presented with more than one symptom, each condition is considered individually.

### **Early myalgia and cramps**

These are severe and more prevalent in proximal muscle, and are aggravated by motion. They often occur in association with at least one other symptom of EMS, such as rash, arthralgias, paresthesias and dysesthesia.

The severity and duration of early myalgia are independent of the dose and duration of L-tryptophan intake.

The characteristics of early myalgia in EMS are similar to those reported in TOS. The relationship of the amount and duration of contaminated oil consumption to myalgia in TOS has not been determined.

## **Myopathy**

Myopathy manifesting mainly as proximal muscle weakness often occurs in association with neuropathic symptoms. As such, it could best be termed neuromyopathy. Proximal muscle weakness is most severe when myositis, muscle necrosis or endomysial inflammation is also present. However, muscle necrosis with endomysial infiltrates is uncommon. The most frequently seen pathologic abnormality is intense fascial and perimysial inflammation.

In the early or intermediate stages of EMS, most patients showed pronounced fasciitis and perimyositis involving mixed inflammatory cells (CD8, CD4, macrophages, monocytes and, rarely, eosinophils). When perimysial inflammation extends to the endomysium or is associated with scattered necrotic fibres, the clinical manifestation of myopathy is more pronounced. Even in such cases, serum levels of creatine kinase are usually normal or mildly elevated while serum levels of aldolase are increased. This phenomenon remains unexplained.

Electromyography frequently shows typical "myopathic" changes associated with denervation secondary to neuropathy.

In patients followed for 24 to 36 months, myalgia, weakness and fatigue subsided in about half and the remainder showed mild to moderate improvement.

TOS shows a similar pattern and distribution of weakness and inflammation, but such changes occurred more during the intermediate phase of the disease.

## **Neuropathy**

In early EMS, symptoms of paresthesias and dysesthesia are reported in about two thirds of cases, but objective signs of sensory deficit or electrophysiologic evidence of neuropathy are seen in only one third of

patients. In some 5 to 10% of patients, neuropathy develops into a more severe, progressive weakness that may involve the respiratory muscles and lower cranial nerves but not the ocular or facial nerves. Severe disability or death may result; this ascending neuropathy has been responsible for many deaths from EMS. The progression of neuropathy may even occur during or after intensive corticosteroid therapy.

Sural nerve biopsy shows predominantly axonal degeneration, increased fibrosis, perineuritis and perivascular inflammation; in later cases, segmental demyelination may be seen. Perivascular inflammation may extend to the vessel wall and occlude the lumen. Electrophysiologic evidence of axonal degeneration is usually evident. Patients sometimes present with mononeuritis multiplex.

In early TOS, early symptoms of neuropathy are absent. However, the progressive form of neuropathy occurring in the late phases of the illness is usually more severe than in EMS and is associated with more severe and widespread muscle wasting and weight loss.

Electrophysiologic and pathologic findings for the two syndromes are identical, with the exception of more intense and prevalent fibrosis in TOS, perhaps due to the relatively late stage of evolution of the disease in these patients.

### **Late cramps and spasm**

More than 20% of EMS patients experience attacks of severe, sudden, explosive and at times disabling muscle cramps and spasms several months after the onset of the disease. These cramps and spasms have a particular predilection for the thoracoabdominolumbar muscles; less commonly they involve the jaw, leg, hand arm and foot muscles. The attacks occur with variable frequency, from a few to many times daily, and duration, from a few seconds to several hours. Such attacks can cause significant disability and anguish for the patient.

Neither the presence or absence of a neuropathy, myopathy or early myalgia, nor the duration and dose of L-tryptophan intake, are predictive of whether a given patient will develop this condition. The cramps resemble no common condition but bear some resemblance to the spasms and cramps reported in the Satoyoshi syndrome, a rare neuromuscular

condition manifesting as alopecia, cramps and diarrhoea. Late cramps and spasms may constitute the only lingering symptom of EMS. They are variably responsive to medications commonly prescribed for this condition; some patients have responded to dantrolene sodium.

The same pattern and degree of pathological involvement of EMS have been observed in TOS. The only difference is perhaps the degree of severity, both clinically and pathologically. No qualitative neuromuscular differences are apparent between the two syndromes.

In TOS, similar late-appearing cramps (up to 10 years after onset of illness), and myoclonic jerks and spasms have occurred in about 50% of patients. Less intense cramps were observed in the intermediate phase (2-4 months after onset of disease). In TOS, the cramps originate at the distal nerve endings and are not of central, spinal or nerve root origin. Similar localization of cramps in EMS has not been performed. The majority of TOS patients are improving but at a very slow rate.

In TOS, membrane stabilizer drugs, such as quinine sulfate, phenytoin and carbamazepine, have been partially effective.

## Respiratory Manifestations

TOS and EMS appear to share a number of respiratory manifestations. These include an acute respiratory illness manifested by pulmonary infiltrates and hypoxemia that was often responsive to corticosteroid therapy, with a few patients progressing to chronic respiratory disease. Pleural effusions are common during the acute phase of both conditions. A small percentage of patients in both groups develop chronic pulmonary hypertension that can be severe and progressive, although it does not usually follow the rapid course characteristic of primary pulmonary hypertension.

Spontaneous improvement in or remission of, chronic pulmonary hypertension occurs in both diseases but is more frequent in patients who have relatively mild to moderate hypertension. A reduced diffusing capacity for carbon dioxide may indicate the presence of a restricted pulmonary vascular bed in TOS, as evidenced by abnormal pulmonary haemodynamics during exercise in this patient population.

However, in EMS, other factors may cause or contribute to a reduction in diffusing capacity, including the concomitant presence of interstitial lung disease. The latter may occur with greater frequency in EMS than in TOS. To date, two patients with EMS-induced pulmonary hypertension underwent lung transplantation in the United States: both died. It is unclear whether the presence of EMS put these patients at a significantly greater risk of death from lung transplantation compared with other patients undergoing this treatment.

The respiratory manifestations of these two diseases nevertheless differ in several ways. First, the acute respiratory process in TOS was characterized by what was described pathologically as interstitial, rather than alveolar, edema without evidence of alveolar deposition of proteinaceous material or neutrophil aggregation. This process bears some similarity to the permeability edema of the adult respiratory distress syndrome (ARDS).

However, the absence of high protein content, haemorrhage or neutrophil aggregation, and the tendency towards a substantial response to corticosteroid therapy and low mortality rate differs somewhat from typical ARDS. In contrast, the acute respiratory process with EMS is more of an acute interstitial pneumonitis that either resolved spontaneously or was highly responsive to corticosteroid therapy. In addition, respiratory muscle dysfunction contributes to pulmonary symptomatology in a significant percentage of EMS patients.

Second, the vascular changes observed in TOS tend to range from mild to severe, on the basis of the Health-Edwards criteria, and included plexiform changes in some patients. In contrast, plexiform lesions have not been reported in EMS patients with pulmonary hypertension.

## Skin Manifestations

Cutaneous manifestations have been noted in approximately 80% of EMS patients. Early cutaneous features included intense pruritis, diffuse morbilliform eruptions, urticaria, livedo reticularis, and in some patients, alopecia.

The morbilliform rash was an early lesion, frequently pruritic. It occurred over the trunk and extremities and was transient. No exfoliation followed its resolution.

Edema was also a frequent early manifestation of EMS, noted in about 50% of cases. The edema was prominent in the extremities, the lower more frequently than the upper, and was very responsive to steroid treatment. Fasciitis often accompanied or followed edema.

Alopecia was reported in 20 to 80% of EMS patients. It affected the entire body, particularly the scalp, and to a lesser extent the extremities, and axillary and the pubic areas. Alopecia was not associated with scarring or significant inflammation. In many cases the alopecia resolved completely.

Another manifestation of EMS, noted in about 20% of cases, was papular mucinosis. It often occurred after L-tryptophan had been discontinued and was frequently associated with generalized pruritis. Small (1-5 mm), flesh-coloured papules were noted more frequently on the extremities than on the trunk. These papules often resolved but have been persistent in some cases. Histopathologic studies have found mucin in the dermis, subcutaneous tissue and fascia.

A characteristic feature of EMS is the scleroderma-like skin seen in approximately 50% of all cases. The scleroderma frequently affected both the extremities and the trunk. Unlike idiopathic scleroderma, the scleroderma-like changes observed in EMS were not accompanied by sclerodactyly, digital ulcerations, Raynaud's phenomenon or nailbed capillary abnormalities. The lesions were generally localized and consisted of morphea, linear scleroderma or combinations of the two. Some patients developed proximal thickening that resembled diffuse scleroderma. They were also frequently accompanied by fasciitis. Histopathologic examination of the skin from such patients showed dermal edema, inflammation and sclerosis, as well as mucinosis.

In general, the skin sclerosis gradually improved. A few serial histopathologic studies suggest gradual resolution of inflammation but persistent dermal and fascial fibrosis. Localized scleroderma-like lesions, specifically morphea, have developed in some patients as long as 3 years after the onset of disease.

One major soft tissue manifestation seen in approximately 50% of EMS patients was fasciitis. Examination of the skin often revealed

subcutaneous induration and puckering, sometimes accompanied by changes of the peau d'orange type and the characteristic groove sign. Fasciitis was sometimes accompanied by limb contractures. Histopathologic evaluation revealed inflammation and sclerosis affecting the fascia and deep dermis, with a cellular infiltrate consisting of macrophages, lymphocytes, mast cells and sometimes eosinophils.

Histopathologically, these changes were very similar to those observed in TOS. Although fasciitis was not as well described in TOS patients, it could well have been present clinically but overlooked histologically because of the fulminant nature of the illness, with major organ involvement in many patients.

Facial cutaneous changes are relatively absent in EMS compared to TOS, in which a characteristic facial appearance was present in the severely affected hospitalized TOS patients. The facial skin involvement in TOS may have been related to the muscle atrophy and subcutaneous atrophy that occurred in association with profound weight loss. TOS patients also appeared to have more frequent acral involvement of the fingers, although these changes may have represented trophic changes related to neuropathy. In contrast, most EMS patients did not have acral changes unless they had severe neuropathy. In such cases the acral changes were probably also due to trophic changes.

TOS patients showed spontaneous improvement in the cutaneous features. EMS patients who have received a variety of medical treatments also showed improvement, but such improvement has also been seen in EMS patients not receiving treatment. Despite overall improvement in cutaneous changes, some EMS patients continue to have papular mucinosis, scleroderma-like skin changes and fasciitis. In addition, some EMS patients are developing later sclerodermal changes, particularly morphea.

## Eosinophil Involvement

The proteins contained within the eosinophil are some of the most basic (pH) substances in the body. These proteins include peroxidase, major basic protein, eosinophilic cationic protein and eosinophil-derived

neurotoxins. The last two, which are members of the RNase family, are very potent proteins that are very toxic to tissue, even in microgram quantities. In addition, eosinophils are known to secrete several cytokines, including several interleukins, T-cell growth factor (TGF), tumour-necrosis factor (TNF) and granulocyte macrophage colony-stimulating factor (GM-CSF).

EMS cases showed significant elevations of eosinophils in peripheral blood and in the granule major basic protein, which is detectable in blood and urine. With steroid treatment, the levels of both eosinophils and granule protein drop, with the latter declining more slowly over time. After treatment is started, granule proteins are still detectable in blood and urine days to weeks after eosinophil counts become normal

In both EMS and TOS patients, intact eosinophils can be seen in tissue in variable numbers alongside large deposits of major basic protein released from previous eosinophil degranulation.

In addition to TOS and EMS, granule proteins and cytokines are released in the hypereosinophil syndrome (HES). Levels of major basic protein in HES cases are even greater than in EMS and TOS.

Eosinophils are among the densest cells in the body, but with activation they become less so as the size, but not the quantity, of their granules decreases. In EMS and HES, eosinophil density declines as a sign of cell activation.

Serum levels of cytokines can be measured in these conditions. In TOS, the predominant cytokine is GM-CSF, whereas in EMS, it is interleukin-5.

A contaminant in implicated L-tryptophan is the peak designated UV-5, phenylamino alanine (PAA). There is a high correlation between the amount of this substance present and the amount of another contaminant 1,1'-ethylidene-bis-[L-tryptophan] (EBT). It is possible that another product, 3-phenylamino-1,2-propanediol, found in oils implicated in TOS could be converted to PAA or vice versa. PAA and phenylaminopropanediol are candidate etiologic agents for both TOS and EMS, respectively.

## Neurocognitive Dysfunction

In one study, EMS patients were initially queried regarding cognitive symptoms and later given extensive neuropsychologic testing. Between 55 and 70% of the EMS patients who filled out and returned questionnaires reported forgetfulness, confusion and concentration difficulty. A total of 24 EMS patients who complained of cognitive problems and 32 healthy controls (age and education matched) underwent neuropsychologic testing to evaluate global intelligence, verbal memory, visual memory, visual motor search, abstract reasoning and motor speed.

Of the EMS patients with cognitive complaints, 62% showed cognitive impairment compared to only 3% of the controls. Verbal memory suffered greatest, as demonstrated on the selective reminding test and the California verbal learning test ( $p > 0.001$ ) level. Patients also did more poorly than controls on visual memory, as measured by the Benton visual retention test, on conceptual reasoning, as measured by the Booklet category test and the Ravens progressive matrices, and on visual motor search, by the trailmaking test part B. Patients and controls differed greatly on motor speed, with the former doing significantly more poorly on the fingertapping test.

However, patients and controls did not differ significantly on measures of premorbid ability, including the information and vocabulary subtests of the Wechsler Adult Intelligence Scale and on a wide-range achievement test. No significant differences were found on verbal fluency and measures of attention and concentration.

Comparison of EMS patients who have demonstrated cognitive impairment with EMS patients who were cognitively intact revealed no group differences with respect to demographic features such as duration of illness, duration of L-tryptophan use, maximum eosinophil count, and interval between onset of neurologic symptoms and discontinuing L-tryptophan. However, EMS patients with cognitive impairment had greater depressive symptomatology compared to EMS patients without cognitive impairment. On a formal psychiatric interview (the structured clinical interview for DSM-III-R disorders, cognitively impaired EMS patients had a 33% rate of current major depression or dysthymia. In comparison, cognitively intact EMS patients had a 0% rate of major depression or

dysthymia. However, this difference between the two groups was not statistically significant.

In conclusion, the results of the study showed that significant cognitive deficits are associated with EMS and that a depression or premorbid personality state is unlikely to be the primary cause.

Measurement of cognitive impairment and determination of premorbid intellectual ability are difficult issues. Possible etiologic factors include the following: an organically based depression and cognitive impairment produced by EMS; depression as a contributing factor to the memory impairment observed; and premorbid personality features that may contribute to the overall cognitive picture.

Although malingering, compensation neurosis or purposeful overrepresentation of cognitive symptoms for purposes of litigation are possibilities, the possibilities of this having occurred were said by some participants to have been minimized by instruments to detect these problems.

In TOS, some 10 to 15% of patients have complained of psychological difficulties including inability to concentrate and memory loss. Most patients have shown gradual improvement.

In TOS, coexisting environmental stress may create some of the observed deficits; this may also be a mechanism for the deficits observed in EMS. For example, insomnia was one reason for taking L-tryptophan. However, in sleep studies of EMS patients conducted by Dr Dan Clauw (see list of participants), polysomnographic abnormalities were not found in patients with significant hypersomnolence. It remains unclear whether the underlying sleep disorder could contribute the observed cognitive symptoms and deficits in EMS.

## Fibromyalgia

About two-thirds of a small cohort of EMS patients under study currently meet the criteria of the American College of Rheumatology criteria for the diagnosis of fibromyalgia. This finding is similar to that in TOS. However, a substantial ambiguity is inherent in this diagnosis, which contributes to

disagreement regarding the premorbid incidence of fibromyalgia in individuals who took L-tryptophan.

At this time, the only conclusion that can be reached is that both TOS and EMS have chronic muscle pain that at this time defies further characterization.

## Animal Models

To date, nine studies have been conducted, most of which are not published. Various strains of rodent have been studied, including Lewis and Sprague-Dawley rats and BALB/C and C57 mice. Depending upon the study, the different strains have been exposed to nonimplicated and implicated L-tryptophan, EBT and PAA, administered by several routes and in variable quantities. No animal model has yet exactly duplicated EMS, and reproducibility with any single model is poor when attempted by different investigators. Several studies, in fact, have been completely negative for any type of inflammatory lesion. However, a recent study by the Mayo Clinic, published only in abstract form, injected synthesized EBT into the Lewis rat; some of the typical histopathologic changes of EMS, along with eosinophilia, were seen in a small number of animals.

Animals seem to develop some aspects of EMS without developing eosinophilia. So far, studies indicate that the intraperitoneal route is more provocative than oral gavage. This is puzzling and suggests that current animal models may not adequately represent the pathophysiology of human disease.

## Overall Conclusion

EMS and TOS are similar in their signs and symptoms, affect the same organs, and share many unusual features and presumed pathophysiologic mechanisms. The strongest similarities between EMS and TOS are eosinophilia and the neuromuscular manifestations. They are both quite distinct from all other reported illnesses.

---

Some differences are seen between these two diseases, especially at the extremes of population distribution, but they tend to be qualitative and minor. One clearcut exception is the difference in early, acute pulmonary manifestations of each disease. These manifestations were more severe and earlier in TOS while they peaked later and were less severe in EMS. However, several months or years into the disease the "average" patient in EMS is very similar to the "average" patient with TOS.

## Future Action

1. Further neurologic studies on the longitudinal course of cognitive function in EMS would be useful. In addition studies using healthy individuals who took L-tryptophan but did not develop EMS as a control group would be most helpful.
2. Longitudinal neurological examinations, electrophysiologic studies and serologic evaluations may become necessary to elucidate the rate of improvement of the neuromuscular syndromes. Patients with the late muscle cramps and spasms should be systematically studied to localize the site and origin of the cramps. This could be done by electrophysiologic studies during sleep, general anaesthesia, and epidural and peripheral nerve blocks, as was done in TOS.
3. Serologic studies using, for example, the newly available antibodies to calcium channel membranes and glutamic acid decarboxylase, may prove useful in determining the pathogenesis of cramps. The development of new neuromuscular symptoms and signs in EMS patients should not be automatically attributed to this condition. All other causes for these symptoms should be sought and excluded.
4. No fully suitable animal model has been found for either TOS, despite a number of studies on different animals, or EMS. Nonetheless, efforts to find such a model should continue.
5. Further longitudinal studies comparing the pathologic features of TOS and EMS would be worthwhile. Additionally, studies evaluating the

potential usefulness of the diffusing capacity as a marker for the development or progression of pulmonary vascular disease would be useful. Long-term studies evaluating the natural history of parenchymal lung disease and pulmonary vascular disease in both TOS and EMS, using noninvasive and invasive measurements, would also be helpful to determine whether similarities exist.

6. A comparison of corresponding pathologic specimens from corresponding times of each disease for similarities and differences would be very useful. A large body of such material on TOS is available. The situation for EMS is more complex, as much material cannot readily be made accessible before litigation is resolved.

7. All EMS patients with pulmonary disease should be vaccinated yearly against influenza. At this time, patients with pulmonary hypertension are advised against pregnancy and against taking oral contraceptives because the condition could worsen.

8. A databank of tissues and serum samples is needed. Efforts already made in this area should be intensified. The experience of the Spanish General Directorate of Research, Planning and Training would be of great assistance.

9. Individual susceptibility in both EMS and TOS is an important issue. For example, in EMS some people developed pulmonary hypertension and others did not. In TOS, not all people with apparently the same oil exposure developed TOS. Studies to elucidate these differences are encouraged.

10. Clinical studies on EMS should be encouraged to standardize their procedures: for example, the use of standard tests given at specified intervals.

11. Efforts to identify and encourage possible cooperative studies in TOS and EMS should be intensified.

12. A meeting in 18 to 24 months is recommended for follow up of these recommendations and to evaluate further the similarities and differences in the clinical progression of the two diseases.

*Annex 1***PARTICIPANTS****Temporary Advisers**

- Dr Ignacio Abaitua Borda  
Toxic Oil Syndrome Programme, Subdirección General de Formación y  
Difusión de la Investigación, Madrid, Spain
- Dr Dan Clauw  
Division of Rheumatology, Georgetown University Medical Center,  
Washington, DC, USA
- Dr Josefa Díaz de Atauri y Rodríguez de los Ríos  
Pulmonary Medicine Department, Hospital "12 de Octubre", Madrid,  
Spain
- Dr Francisco Domínguez Moronta  
Internal Medicine, Hospital Clínico Universitario, Salamanca, Spain
- Dr Joseph Duffy  
Department of Rheumatology, Mayo Clinic, Rochester, Minnesota, USA
- Dr Vicenta Faro Leal  
Gastroenterology Department, Hospital Ramón y Cajal, Madrid, Spain
- Dr Gerald Gleich  
Mayo Medical School, Mayo Clinic, Rochester, Minnesota, USA
- Dr Agustín Gómez de la Cámara  
Toxic Oil Syndrome Programme, Subdirección General de Formación y  
Difusión de la Investigación, Madrid, Spain
- Dr Miguel Ángel Gómez Sánchez  
Cardiology Department, Hospital "12 de Octubre", Madrid, Spain

Dr Roy Goulding

36 Ashley Court, Morpeth Terrace, London, United Kingdom

Dr Yadollah Harati

Baylor College of Medicine, Medical Center, Houston, Texas, USA

Dr Phillip A. Hertzman

Los Alamos Medical Center, Los Alamos, New Mexico, USA

Dr Maravillas Izquierdo Martínez

Internal Medicine, Hospital "12 de Octubre", Madrid, Spain

Dr Miguel Angel Jiménez Arriero

Psychiatry Department, Hospital "12 de Octubre", Madrid, Spain

Dr Lee Kaufman

Department of Medicine, State University of New York, Stony Brook, New York, USA

Dr Edwin Kilbourne

Health Studies Branch, Division of Environmental Hazards and Health Effects, Center for Environmental Health and Injury Control, Centers for Disease Control, Atlanta, Georgia, USA

Dr Lauren Krupp

Department of Neurology, State University of New York, Stony Brook, New York, USA

Dr Carlos Lahoz

Immunology, Fundación Jimenez Diaz, Clínica de la Concepción, Madrid, Spain

Dr Francisco Martínez Tello

Anatomic Pathology Department, Hospital "12 de Octubre", Madrid, Spain

Dr David Masur

Montefiore Medical Center, Bronx, New York, USA

Dr Thomas Medsger

Division of Rheumatology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Dr Julio Nadal

Internal Medicine Department, Hospital General de Catalunya, Barcelona, Spain

- 
- Dr Rossanne Philen  
Health Studies Branch, Division of Environmental Hazards and Health  
Effects, Center for Environmental Health and Injury Control, Centers for  
Disease Control, Atlanta, Georgia, USA
- Dr Theodore Pincus  
Department of Medicine, Vanderbilt University, Medical Center North,  
Nashville, Tennessee, USA
- Dr Manuel Posada de la Paz  
Toxic Oil Syndrome Programme, Subdirección General de Formación y  
Difusión de la Investigación, Madrid, Spain
- Dr Lewis Rubin  
Division of Pulmonary and Critical Care, University of Maryland  
Medical School, Baltimore, Maryland, USA
- Dr Roberta Seidman  
State University of New York, Stony Brook, New York, USA
- Dr Richard Silver  
Medical University of South Carolina, Charleston, South Carolina, USA
- Dr Luis Soldevilla Benito  
Toxic Oil Syndrome Programme, Subdirección General de Formación y  
Difusión de la Investigación, Madrid, Spain
- Dr José Antonio Vaquero Ruipérez  
Neurology Department, Hospital Universitario Príncipe de Asturias,  
Campus Universitario, Madrid, Spain
- Dr John Varga  
Division of Rheumatology, Jefferson Medical College, Philadelphia,  
Pennsylvania, USA

### Observers

- Dr Peter Gorevic  
Division of Allergy, Rheumatology and Clinical Immunology, State  
University of New York, Stony Brook, New York, USA

Dr Barry Gruber

Division of Allergy, Rheumatology and Clinical Immunology, State  
University of New York, Stony Brook, New York, USA

Dr Lori A. Love

Center for Food Safety and Applied Nutrition, Food and Drug  
Administration, Bethesda, Maryland, USA

Dr David Michelson

Unit on Neuroendocrine Immunology and Behavior, Clinical  
Neuroendocrinology Branch, National Institute of Health, Bethesda,  
Maryland, USA

Dr Nancy Peress

State University of New York, Stony Brook, New York, USA

Dr Leon Sokoloff

State University of New York, Stony Brook, New York, USA

## **World Health Organization**

### ***Regional Office for Europe***

Ms Elaine C. Grandjean

Project Administrator, Special Project on the Toxic Oil Syndrome

Ms Jette Gents

Secretary, Special Project on the Toxic Oil Syndrome

