Reviews of Environmental Contamination and Toxicology

VOLUME 200
Foreword

International concern in scientific, industrial, and governmental communities over traces of xenobiotics in foods and in both abiotic and biotic environments has justified the present triumvirate of specialized publications in this field: comprehensive reviews, rapidly published research papers and progress reports, and archival documentations. These three international publications are integrated and scheduled to provide the coherency essential for nonduplicative and current progress in a field as dynamic and complex as environmental contamination and toxicology. This series is reserved exclusively for the diversified literature on “toxic” chemicals in our food, our feeds, our homes, recreational and working surroundings, our domestic animals, our wildlife and ourselves. Tremendous efforts worldwide have been mobilized to evaluate the nature, presence, magnitude, fate, and toxicology of the chemicals loosed upon the earth. Among the sequelae of this broad new emphasis is an undeniable need for an articulated set of authoritative publications, where one can find the latest important world literature produced by these emerging areas of science together with documentation of pertinent ancillary legislation.

Research directors and legislative or administrative advisers do not have the time to scan the escalating number of technical publications that may contain articles important to current responsibility. Rather, these individuals need the background provided by detailed reviews and the assurance that the latest information is made available to them, all with minimal literature searching. Similarly, the scientist assigned or attracted to a new problem is required to glean all literature pertinent to the task, to publish new developments or important new experimental details quickly, to inform others of findings that might alter their own efforts, and eventually to publish all his/her supporting data and conclusions for archival purposes.

In the fields of environmental contamination and toxicology, the sum of these concerns and responsibilities is decisively addressed by the uniform, encompassing, and timely publication format of the Springer triumvirate:

*Reviews of Environmental Contamination and Toxicology* [Vol. 1 through 97 (1962–1986) as Residue Reviews] for detailed review articles concerned with any aspects of chemical contaminants, including pesticides, in the total environment with toxicological considerations and consequences.
Bulletin of Environmental Contamination and Toxicology (Vol. 1 in 1966) for rapid publication of short reports of significant advances and discoveries in the fields of air, soil, water, and food contamination and pollution as well as methodology and other disciplines concerned with the introduction, presence, and effects of toxicants in the total environment.

Archives of Environmental Contamination and Toxicology (Vol. 1 in 1973) for important complete articles emphasizing and describing original experimental or theoretical research work pertaining to the scientific aspects of chemical contaminants in the environment.

Manuscripts for Reviews and the Archives are in identical formats and are peer reviewed by scientists in the field for adequacy and value; manuscripts for the Bulletin are also reviewed, but are published by photo-offset from camera-ready copy to provide the latest results with minimum delay. The individual editors of these three publications comprise the joint Coordinating Board of Editors with referral within the Board of manuscripts submitted to one publication but deemed by major emphasis or length more suitable for one of the others.

Coordinating Board of Editors
Preface

The role of Reviews is to publish detailed scientific review articles on all aspects of environmental contamination and associated toxicological consequences. Such articles facilitate the often-complex task of accessing and interpreting cogent scientific data within the confines of one or more closely related research fields.

In the nearly 50 years since Reviews of Environmental Contamination and Toxicology (formerly Residue Reviews) was first published, the number, scope and complexity of environmental pollution incidents have grown unabated. During this entire period, the emphasis has been on publishing articles that address the presence and toxicity of environmental contaminants. New research is published each year on a myriad of environmental pollution issues facing peoples worldwide. This fact, and the routine discovery and reporting of new environmental contamination cases, creates an increasingly important function for Reviews.

The staggering volume of scientific literature demands remedy by which data can be synthesized and made available to readers in an abridged form. Reviews addresses this need and provides detailed reviews worldwide to key scientists and science or policy administrators, whether employed by government, universities or the private sector.

There is a panoply of environmental issues and concerns on which many scientists have focused their research in past years. The scope of this list is quite broad, encompassing environmental events globally that affect marine and terrestrial ecosystems; biotic and abiotic environments; impacts on plants, humans and wildlife; and pollutants, both chemical and radioactive; as well as the ravages of environmental disease in virtually all environmental media (soil, water, air). New or enhanced safety and environmental concerns have emerged in the last decade to be added to incidents covered by the media, studied by scientists, and addressed by governmental and private institutions. Among these are events so striking that they are creating a paradigm shift. Two in particular are at the center of ever-increasing media as well as scientific attention: bioterrorism and global warming. Unfortunately, these very worrisome issues are now super-imposed on the already extensive list of ongoing environmental challenges.

The ultimate role of publishing scientific research is to enhance understanding of the environment in ways that allow the public to be better informed. The term “informed public” as used by Thomas Jefferson in the age of enlightenment
conveyed the thought of soundness and good judgment. In the modern sense, being “well informed” has the narrower meaning of having access to sufficient information. Because the public still gets most of its information on science and technology from TV news and reports, the role for scientists as interpreters and brokers of scientific information to the public will grow rather than diminish. Environmentalism is the newest global political force, resulting in the emergence of multi-national consortia to control pollution and the evolution of the environmental ethic. Will the new politics of the 21st century involve a consortium of technologists and environmentalists, or a progressive confrontation? These matters are of genuine concern to governmental agencies and legislative bodies around the world.

For those who make the decisions about how our planet is managed, there is an ongoing need for continual surveillance and intelligent controls, to avoid endangering the environment, public health, and wildlife. Ensuring safety-in-use of the many chemicals involved in our highly industrialized culture is a dynamic challenge, for the old, established materials are continually being displaced by newly developed molecules more acceptable to federal and state regulatory agencies, public health officials, and environmentalists.

Reviews publishes synoptic articles designed to treat the presence, fate, and, if possible, the safety of xenobiotics in any segment of the environment. These reviews can either be general or specific, but properly lie in the domains of analytical chemistry and its methodology, biochemistry, human and animal medicine, legislation, pharmacology, physiology, toxicology and regulation. Certain affairs in food technology concerned specifically with pesticide and other food-additive problems may also be appropriate.

Because manuscripts are published in the order in which they are received in final form, it may seem that some important aspects have been neglected at times. However, these apparent omissions are recognized, and pertinent manuscripts are likely in preparation or planned. The field is so very large and the interests in it are so varied that the Editor and the Editorial Board earnestly solicit authors and suggestions of underrepresented topics to make this international book series yet more useful and worthwhile.

Justification for the preparation of any review for this book series is that it deals with some aspect of the many real problems arising from the presence of foreign chemicals in our surroundings. Thus, manuscripts may encompass case studies from any country. Food additives, including pesticides, or their metabolites that may persist into human food and animal feeds are within this scope. Additionally, chemical contamination in any manner of air, water, soil, or plant or animal life is within these objectives and their purview.

Manuscripts are often contributed by invitation. However, nominations for new topics or topics in areas that are rapidly advancing are welcome. Preliminary communication with the Editor is recommended before volunteered review manuscripts are submitted.

Summerfield, North Carolina

D.M.W.
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Illnesses Associated with Chloropicrin Use in California Agriculture, 1992–2003

Michel Oriel, Susan Edmiston, Sheryl Beauvais, Terrell Barry, and Michael O’Malley

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1 Introduction

Because methyl bromide use is limited by international treaty (Albritton et al. 1998; U.S. EPA 2004), use of metam-sodium, chloropicrin, and other fumigants have increased (Fig. 1), and have been accompanied by multiple community illness episodes (O’Malley et al. 2004a, b, 2005). The purpose of this article is to review the California experience with the use of chloropicrin as an active ingredient in agricultural fumigations between the years 1992 and 2003.
2 Chloropicrin: History and Essential Background

2.1 History

Chloropicrin was initially synthesized in 1848 by addition of bleaching powder to picric acid, and was initially patented in 1908 for use as an insecticide in the fumigation of stored grains and for nematode soil treatments.

During WW I, chloropicrin was used as a tear gas and was the subject of several experimental studies with small numbers of volunteer subjects. In 1921, Fries and West reported on the ocular dose response for four subjects: the time to involuntary eye closure for chloropicrin concentrations was between 2 and 38 sec, at concentrations between 2 and 20 ppm (Fries and West 1921). Concentrations below 1–2 ppm produced “considerable blinking” but not eye closure. Flury and Zernik (1931) summarized the results of German studies (original citation by Gildemeister and Heubner 1920) on chloropicrin. These studies demonstrated that chloropicrin concentrations of 0.3–3.7 ppm produce involuntary eye closure within 3–30 sec. Concentrations of 15 ppm could not be tolerated by unhabituated subjects for longer than 1 min (Flury and Zernik 1931). In addition to intense eye irritation, wartime exposure to chloropicrin was associated with coughing and severe gastrointestinal effects, which included persistent nausea, vomiting, colic, and diarrhea (Fries and West 1921; Prentiss 1937).
2.2 Registered Products

Chloropicrin is classified as a Toxicity Category I substance and is a restricted use pesticide. It is labeled with the signal word “Danger” (Meister 2003). Applications occur at least 4 d prior to planting, with liquid fumigant injected into soil approximately 6–10 in. below the surface. Target pests include soilborne fungi, nematodes, and soil insects (Wilhelm 1996; Meister 2003).

As of May 2006, there were 48 formulations containing chloropicrin as an active ingredient that were actively registered in California (Department of Pesticide Regulation (DPR) 2006). These included 13 formulations with no other active ingredient (concentrations 94–100% chloropicrin), and 11 formulations containing combinations of dichloropropene (concentrations 37.6–82.9%) and chloropicrin (concentrations 15–60%). Although the Montreal Protocol was to have eliminated use of methyl bromide by the end of 2005, there were 24 formulations of chloropicrin extant (concentrations 24–55%) that contained methyl bromide (concentrations 33–80%) as of February 2006. Another use of chloropicrin is as a warning agent in sulfuryl fluoride structural applications, although it is introduced to the structure at the time of fumigation rather than being mixed with the sulfuryl fluoride in the formulation process.

During 2004, chloropicrin was the eighth most widely used pesticide in California (all sites combined) (DPR 2005). In the USA, chloropicrin moved from being the 39th most commonly used pesticide in the agricultural market sector in 1993, to being the 14th most used, in 1999 (Donaldson and Kiely 2002).

2.3 Physical and Chemical Properties

Chloropicrin is the common name for the chemical trichloronitromethane, or nitrochloroform. It is a colorless to faint-yellow oily liquid with a strong odor that can be described as pungent, sweet, and irritating, or resembling flypaper (Prentiss 1937; Hayes and Lawes 1991). Chloropicrin has a molecular weight of 164.4 D (Daltons), a specific gravity of 1.66 at 20°C, and a density of 1.65 g cm⁻³ at 20°C. It has a boiling point of 112°C, melting point of 64°C, and a vapor pressure of 18.3 mmHg at 20°C (Great Lakes Chemical Corporation 2001). It is practically insoluble in water (0.18 g/100 g at 20°C) but is miscible with benzene, absolute alcohol, and carbon disulfide. Decomposition of chloropicrin may release the following toxic gases and vapors: phosgene, chlorine, carbon monoxide, nitrosyl chloride, and oxides of nitrogen (American Conference of Governmental Industrial Hygienists 1996).

2.4 Legal Exposure Limits

The current threshold limit value (TLV), set for chloropicrin in 1959, is 0.1 ppm for an 8-hr time-weighted average exposure. Documentation for this standard cites
a review by Stokinger (1978), based upon a brief review of animal and human studies on chloropicrin published in 1931 (Flury and Zernik 1931). The 1931 review summarized WWI era human studies as follows:

... concentrations of 0.3 to 0.37 ppm resulted in eye irritation in 3 to 30 sec, depending on individual susceptibility.

A concentration of 15 ppm could not be tolerated longer than 1 min, even by individuals accustomed to chloropicrin.

In 1959, the TLV was reduced to 0.1 ppm. According to Stokinger, this was done “to provide greater protection from eye irritation in all workers and to ensure against potential pulmonary changes”. “It [the 0.1 ppm TLV] is below concentrations detectable by odor or irritation” (Stokinger 1978).

3 Chloropicrin: Exposure and Effects

3.1 Volunteer Studies

Experimental studies with pesticides and other industrial products are often controversial, particularly when nonpharmaceuticals (such as pesticides) are intentionally administered to humans, regardless of potential study benefits (Bates et al. 2005; Boxer and Waxman 2005; Kaiser 2003). Controversy surrounded a human volunteer study (Cain 2004) performed on the irritant effects of chloropicrin (Lee and Clark 2005). Notwithstanding, the Cain study demonstrated chloropicrin effects below the current TLV.

Key findings of this study are summarized below:

• The median instantaneous odor detection threshold for all subjects was 700 ppb. The perception of odor diminished with prolonged exposure, while the perception of irritation increased.

• For brief exposures (5–30 sec), eye irritation (or at least “chemesthesis” – detection of exposure by the eye) occurred in 50% of volunteer subjects exposed to 700 ppb of chloropicrin. Of the 62 subjects tested, 10–15% (depending upon the site of exposure) failed to detect 1,200 ppb of chloropicrin (the highest concentrations tested in the study).

• For exposures lasting 20 min, the minimum concentration detectable by 50% of the subjects was 75 ppb. The no-observed-effect-level (NOEL) for this portion of the study was 50 ppb. One-hr exposures to 100 and 150 ppb produced subjective eye irritation in most subjects. Using a standard tenfold uncertainty factor (Extoxnet 2006), an estimated NOEL for a 1-hr exposure to chloropicrin (calculated from the 100 ppb LOEL (lowest-observed-effect-level)) was 10 ppb.

• In the subjects studied (selected for absence of asthma, allergic rhinitis, and other common respiratory conditions), respiratory irritation was not quantifiable for brief exposures above 1 ppm. Similarly, no upper or lower respiratory symptoms
were noted in either the 20 min (75 ppb), or 60 min (100 and 150 ppb) exposures (Cain 2004).

The distinction between chemesthesis and irritation made by Cain is not made by other specialists in sensory irritation. A review by Dalton (2001), for example, uses the terms “chemesthesis” and “irritation” interchangeably. She makes the point that the onset of sensory irritation is highly influenced by subjective factors. In this regard, the subjective experience of a paid volunteer, in an experimental study, probably would be different from the subjective experience of someone accidentally exposed to the same concentration of an irritant in the workplace, or as the result of an unexpected environmental exposure.

### 3.2 Exposure Monitoring Studies

Exposure monitoring studies of preplant soil treatment using chloropicrin fumigations have been conducted by product manufacturers and by the state of California; worker exposure and/or downwind air concentrations were recorded after these treatments. In addition, though not elaborated here, attempts have been made in a few exposure studies of structural fumigations to either document “warning” concentrations of chloropicrin inside treated structures, or to record levels of post-application chloropicrin residues (Fong 2004).

#### 3.2.1 Worker Monitoring

In 1982, workers were monitored, in the breathing zone, during two preplant soil applications (Maddy et al. 1984a). The first involved applying a mixture of 33% chloropicrin and 67% methyl bromide (300 lb of formulated product/A). The second application employed 75% methyl bromide/25% chloropicrin (275 lb of formulated product/A). The monitored workers included two application rig drivers, two rig “co-pilots” (seated at the back of the rig, and responsible for ensuring that the injectors and other application equipment were operating correctly), and a “shoveler” (responsible for covering the edges of the application tarp with soil) at the second application site only.

Drivers and copilots were exposed to breathing-zone concentrations of methyl bromide (0.4–6.3 ppm), and chloropicrin (from the < 1 ppb limit of detection to 181 ppb). The “shoveler”, monitored for 45 min, had exposure to breathing zone concentrations of 0.7 ppm of methyl bromide and 45 ppb of chloropicrin (Maddy et al. 1984a). Methyl bromide measurements were associated with “break through” in the sampling tubes and may have underestimated the actual concentrations present (Maddy et al. 1984a).

Subsequently, soil fumigation treatments, monitored in August and September, 1983 (Maddy et al. 1984b), involved the same two products (75% methyl bromide/25%
chloropicrin and 67% methyl bromide/33% chloropicrin), but demonstrated markedly higher exposures. Drivers were exposed to breathing-zone methyl bromide concentrations between 3.1 and 38 ppm; chloropicrin exposure ranged between 90 and 1,544 ppb.

Exposure monitoring studies sponsored by the Chloropicrin Manufacturers’ Task Force were reported as estimated 8-hr time-weighted-average exposures (Rotandaro 2004). The highest chloropicrin concentrations were found for drivers in the shank-bedded nontarped method (Sites 13–15); the arithmetic mean + standard deviation (SD) concentration was 255 + 120 µg m\(^{-3}\) (38 ppb). Concentrations measured outside the cabs for these drivers were higher; the two replicates gave results of 208 µg m\(^{-3}\) (31.2 ppb) and 1,020 µg m\(^{-3}\) (153 ppb), for a mean of 614 µg m\(^{-3}\) (92.1 ppb).

During shank broadcast applications, average exposures to rig drivers were 118 µg m\(^{-3}\) (17.7 ppb). Average exposures for soil sealers (workers who follow the applicator, driving a second tractor equipped with soil disc and cultipacker, or similar device) was 66.6 µg m\(^{-3}\) (9.9 ppb). Exposures to re-entry workers (“soil shapers”, tarp punchers and pipe layers) ranged from 8.84 to 75.9 µg m\(^{-3}\) (1.36–11.25 ppb) (Rotandaro 2004).

### 3.2.2 Downwind Monitoring

In 1982 (Maddy and Gibbons 1983), methyl bromide and chloropicrin levels were monitored at three application sites in Southern California, 25 ft downwind from a shallow injection application of methyl bromide and chloropicrin. Resultant residue levels of methyl bromide ranged from below the limit of detection (<22 ppb) to 634 ppb. The peak levels of chloropicrin (in samples collected for 45 min) detected at the three sites were 33, 76, and 106 ppb, at varying intervals after the application. Only limited data were contained in the report about the application mixture and the environmental conditions.

In 1983, Maddy et al. (1984c) monitored chloropicrin and methyl bromide residues for 1 hr 50 ft downwind from two preplant soil applications. The specific mixture applied to the treated field and the details of the environmental conditions were not specified in the report. Methyl bromide concentrations ranged from below the limit of detection (<3 ppb) to 814 ppb, and chloropicrin concentrations varied from < 1 ppb to 81 ppb.

In 1996, the Chloropicrin Manufacturers’ Task Force submitted monitoring data to the California Department of Pesticide Regulation on preplant soil fumigations conducted during 1995 near Phoenix, AZ. Monitoring was conducted for a 6-hr duration up to 180 ft downwind of the applications, which were conducted using four different methods (Beard et al. 1996). Samplers were typically located at 60-, 120-, and 180-ft downwind from the site of application. The results are summarized below:

1. **Broadcast-untarped application (171lb/A effective broadcast rate).** Three samplers on the east transect showed 6-hr time-weighted average concentrations of 0.27 ppm, 0.25 ppm, and 0.26 ppm at 60 ft, 120 ft, and 180 ft, respectively.
2. **Bedded-untarped application (86 lb/A effective broadcast rate)**. During the first 6-hr sampling period, the concentrations in the 60-ft and 120-ft samplers on the north transect were 0.26 ppm and 0.18 ppm, respectively. The concentration at the 60-ft west sampler was 0.16 ppm. During the second 6-hr period, following the 6–12-hr application, the north transect showed air concentrations for the 60-, 120-, and 180-ft samplers of 0.22 ppm, 0.15 ppm, and 0.16 ppm, respectively.

3. **Bedded-tarped application (189 lb/A effective broadcast rate)**. During the period 6–12 hr after application, the 60-ft east sampler showed 0.15 ppm and the 60-ft south sampler showed 0.18 ppm. Concentrations exceeding 0.15 ppm were observed for samplers at 60, 120, and 180 ft. During the 24–30-hr sampling period following application, the 60-, 120-, and 180-ft east samplers showed 0.19 ppm, 0.19 ppm, and 0.16 ppm, respectively. The 60-ft south sampler showed 0.19 ppm. During the 30–36 hr following application sampling (night and evening hours), the 60-, 120-, and 180-ft south samplers showed 0.27 ppm, 0.21 ppm, and 0.15 ppm, respectively. For the same application rates bed-tarp applications have much higher flux than does broadcast-tarp.

4. **Broadcast-tarped application (332 lb/A effective broadcast rate)**. Even though the broadcast-tarped application rate (332 lb/A) was 1.75 times higher than the effective broadcast rate of the bed-tarp application (189 lb effective broadcast rate/A), the measured concentrations of chloropicrin were generally lower than those associated with the bedded tarped application. There were several samplers that showed measured concentrations between 0.10 and 0.15 ppm. In studies with methyl bromide, differences in air concentrations and flux between bed-tarp and broadcast-tarp methyl bromide applications were also observed.

### 3.2.3 Flux Measurements

Onsite measurements made during the study (Beard et al. 1996) also allowed for estimation of flux (kilogram of evaporated chloropicrin/A/24 hr); with an estimation of flux, calculation of chloropicrin dispersion at downwind distances greater than those actually monitored (e.g., with the Industrial Source Complex (US EPA OAQPS 1995; O’Malley et al. 2004a) (ISC3 model) was possible. Flux estimates gleaned from the study are summarized in Table 1.

The Chloropicrin Manufacturers’ Task Force submitted the results of an occupational exposure study conducted in 2004, in which downwind worker monitoring results were reported at 2 of 27 sites. For site 16, 4.5 A of an 8.67-A field was treated with chloropicrin EC (Emulsifiable Concentrate) at 300 lb/A by surface drip (tarped and bedded) application. During the first 48 hr after application, samples were collected at 4-hr intervals using XAD-4® resin tubes. After 48 hr, the sampling interval duration varied between 9 and 13 hr. For the initial 4-hr sampling interval, the measured concentration of chloropicrin was slightly less than 0.04 ppm (40 ppb). For the second 4-hr interval, the measured concentration was approximately 0.055 ppm (55 ppb). Peak off-site flux (70 µg of chloropicrin/m²/sec) was also measured during