

The power of the industrial product lobby: controversy, doubt, contradiction, lies and deceit and attacks on the Ramazzini Institute

Il potere della lobby industriale: polemiche, dubbi, contraddizioni, inganni e menzogne e gli attacchi all'Istituto Ramazzini

Myron A. Mehlman

Mt. Sinai School of Medicine, New York, NY, USA

Summary

Over the years, industry and industry-paid consultants have provided studies that show that their chemicals are safe. Efforts include use of laboratories such as the Industrial Biotest Laboratory that were shown in 1976 to have falsified experimental data to the Shanghai Health Study proposed and funded by the petroleum industry to prove that benzene exposure is not harmful and benzene is non-carcinogenic. Studies reported by industry consultants have been re-evaluated by independent scientists, and flaws in data collection or data analysis have been published. Industry has long attempted to mischaracterize studies by the Ramazzini Foundation (RF), founded by Cesare Maltoni (deceased). Through the 1970's to the present time, the RF has been scrutinized by governmental regulatory bodies, studies have been duplicated by the National Toxicology Program, and studies reported by the RF have been consistently found to be accurate. Recently, industry has attempted to refute RF animal studies of

Riassunto

Nel corso degli anni, l'industria e consulenti pagati dall'industria, hanno condotto studi per dimostrare che i prodotti chimici sono sicuri. Tali sforzi includono l'uso di laboratori quali l'Industrial Biotest Laboratory, che nel 1976 è stato denunciato per aver falsificato dati sperimentali dello Shanghai Health Study, studio sponsorizzato e finanziato dall'industria petrolifera per dimostrare che l'esposizione a benzene non è nociva e che il benzene non è cancerogeno. Gli studi riportati dai consulenti dell'industria sono stati riesaminati da scienziati indipendenti i quali pubblicarono le imprecisioni nella raccolta dei dati o nell'analisi dei dati. L'industria ha lungamente tentato di screditare gli studi della Fondazione Ramazzini (FR), fondata da Cesare Maltoni (deceduto). A partire dagli anni '70 fino ad oggi, la FR è stata sottoposta a vari accertamenti da parte di enti governativi preposti, i suoi studi sono stati ripetuti anche dal National Toxicology Program e gli studi pubblicati dalla FR sono stati costantemente ritenuti accurati. Di recente

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Address/Indirizzo: Myron A. Mehlman, Ph.D., 7 Bouvant Drive, Princeton, NJ 08540 USA - Tel. 609-683-1493 - E-mail: mehlman@comcast.net

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aspartame and MTBE that show increases in lymphohematological neoplasms by stating that animals are afflicted with bacterial infections that cause inflammation that resembles neoplasms. RF data and slides that address this point, as well as repeated statistical analysis of RF data, show that this is not so. The data stand. *Eur. J. Oncol.*, 14 (4), 223-229, 2009

Key words: industry practices, MTBE, aspartame, benzene, vinyl chloride, good science ED01 Study

Cancer studies in animals conducted by independent, high quality scientific research institute, the Ramazzini Foundation (RF) in Italy on chemicals or chemical products that are produced, distributed, and sold by corporations and generate substantial corporate profit are, without exception, criticized by product defense consultants. These product defense consultants skew, distort, and change published scientific and technical literature and create, manufacture doubt, market scientific uncertainty and influence regulatory agencies, public opinion, and the judiciary to the advantage and economic benefit of the manufacturers who produce and market dangerous and cancer-causing chemicals that threaten the health and lives of the public.

This they do by claiming that the link between toxic, cancer-causing chemicals is unclear, uncertain, incomplete, biased, flawed and that there is a critical need for more reliable studies. They also claim that there is a need for their views of “good science” and “sound science” and no independent scientific entities, such as the RF, academia, or governmental laboratory can conduct such science. This “good science” can only be conducted in laboratories such as Industrial Biotest Laboratory (IBT), corporate laboratories, or in some academic laboratories paid by industry. With strict contracts, manufacturers are certain that these studies will produce results with preordained conclusions prior to the start of the study.

l’industria ha tentato di contestare gli studi sperimentali condotti dalla FR sull’aspartame e l’MTBE, che dimostrano un incremento delle neoplasie linfoematologiche, sostenendo che gli animali erano affetti da infezioni batteriche che davano origine a infiammazioni somiglianti a neoplasie. I dati e i preparati della FR riguardanti questo punto, così come le ripetute analisi statistiche dei dati forniti dalla FR, dimostrano che non è così. I dati parlano di per sé. *Eur. J. Oncol.*, 14 (4), 223-229, 2009

Parole chiave: pratiche industriali, MTBE, aspartame, benzene, cloruro di vinile, Studio ED01 good science

John Bailar III, (1), a highly distinguished biostatistician and member of the National Academy of Science, stated that, “Science conducted by manufacturers puts a premium on bad science that guarantees negative results due to small sample size, poor protocols, and fuzzy statistics” and, of course, “extreme bias in favor of the manufacturers” (2).

In his book entitled “*Doubt is Their Product. How Industry’s Assault on Science Threatens Your Health*”, David Michaels (3) showed that all eleven studies conducted by or for chemical companies showed no harmful effects whereas studies funded by governmental research laboratories, or by academia reported that 84 of 109 studies on the same chemicals showed harmful effects. This is not a surprise because product defense companies almost always produce, “an arbitrary, capricious, and specious re-analysis of studies conducted by independent scientists whose studies show carcinogenicity of dangerous, cancer-causing chemicals”.

Good Science, Sound Science

“Good science” and “sound science” are corporate code words developed initially by Big Tobacco and now frequently used by manufacturers of toxic, dangerous chemicals to defend and protect profits. Good science is frequently employed by product defense specialists and means that only studies that

show no harmful effects are good and all other studies, i.e., those which find cancer from exposure to chemicals are biased or bad science or “junk science”.

IBT Laboratory

Tests performed for industry by IBT, were considered by product defense experts as “good science” or “sound science”. In the 1970’s, IBT conducted 35-40% of testing in U.S. During this time, Industry submitted IBT test results to regulatory agencies in support of safety of thousands of products. In 1976, IBT lab was exposed as a fraud by the FDA. Fagin *et al.* (4) in their book entitled “*Toxic Deceptions: How the Chemical Industry Manipulated Science Bends the Law and Endangers Your Health*”, from the Center for Public Integrity, Washington, DC, reported on the practices of IBT. Evidence showed that numerous studies were fraudulent due to use of small sample size, short test periods, listing sick animals as healthy, and/or concealing animal death.

Studies conducted by Belpoggi and Soffritti of the RF are criticized by a throng of product defense, industry-paid consultants to create uncertainties while practicing the same methods as used by IBT Laboratories, which conducted many studies for the MTBE manufacturing industry.

Similar critiques and accusations by product defense consultants have occurred for four decades on benzene, vinyl chloride, trichloroethylene, formaldehyde, and many other chemicals which, today, are well known and accepted carcinogens in humans. These critiques of scientific facts are troublesome. As John Bailar III (1) described, “There are many ways to mislead readers and users of the scientific literature without resort to fraud or other kinds of lying. These include the artful choice of topics for study, framing the question so as to reach a predetermined conclusions, weak protocols, undisclosed omissions of data points and/or relevant information, and deliberate distortions in the process of data reduction and presentation... Scientists, users of science, and the public should be aware of the potential for deliberate distortion of scientific records, learn how to recognize it and

guard against it”. These data manipulations are highly detrimental to public health, especially to pregnant women, infants, people on medication, and individuals with chronic diseases. Many will suffer and some will die.

Critique by Independent Scientists of Studies Done by Industry Consultants: True Junk Science

1. This study, conducted by Mobil Oil Corporation’s Gerhard K. Raabe and Otto Wong, consultant for Mobil, entitled “An Updated Mortality Study of Workers at the Beaumont, Texas Refinery, 1945-1987. Report dated December 5, 1994” (5), was done not to identify greatly increased risk to workers but to support Mobil Oil’s position during litigation. Critique of Raabe and Wong (5) (1994) studies included flaws in methodology, statistical analysis, science, and exposure. The study group included many workers, e.g., office staff, accounting groups, and administrators, who were NOT exposed to chemicals. There is no discussion of the limitation of looking only at the number of deaths rather than the incidence of different types of cancers. Some cancers have long survival times while others are associated with early death. This fact also negates the value of looking at time since first employment and the duration of employment. Throughout the report, results for non-white males are not included in tabular form. Statistical analysis does not differentiate between groups of workers who were exposed to benzene vs. other toxic chemicals; this lack of distinction dilutes the population and tends to mask significant results.

The lowering of the lower confidence limit by considering the number “101” significant and “99” not significant is an obvious attempt to downplay the positive results. Only mortality (death) is studied; incidence (number of cases) is not considered. Given these basic flaws, study results are meaningless.

2. As reviewed by Infante (6), “Wong and Raabe from the Mobil Oil Corporation have recently said that benzene exposure causes acute myelocytic leukemia only...”. It is difficult to reconcile Wong’s opinion in light of his own study results reported in the British Journal of Industrial Medicine in

1987...”. Wong and Raabe (7) have recently concluded that a range of 400-500 ppm-years of benzene exposure is the threshold for leukemia. The data in the Dow study (8, 9) and Wong’s own study (10) clearly contradict this statement”.

3. McMichael (11) criticized the study of Thorpe (12) of 38,000 petroleum workers potentially exposed to benzene that showed no evidence of significant leukemia excess as a result of exposure to benzene. This interpretation ignores the comparison of exposed workers with control workers (from the same facilities, but not exposed to benzene); the exposed group had a two-fold risk for leukaemia relative to the non-exposed group. The choice of an appropriate comparison is an important issue. In a number of studies, analyses based on comparisons with the general population failed to detect an increased risk for lympho-haematopoietic cancer or leukaemia.

In the same citation, McMichael (11) criticized the cohort study of eight oil refineries in Britain by Rushton & Alderson (13) because the initial calculations of the leukemia SMR based on a comparison with the general population revealed no significant excess. However, subsequent analyses by McMichael (12) that took account of variations in benzene exposure between categories of workers revealed positive associations with leukemia.

4. Goldstein & Shalot (14) state regarding the Bergsagel (15) article:

“The evidence cited by Bergsagel *et al.* does not at all support their conclusion that ‘there is no causal relationship between exposure to benzene or benzene-containing solvents and multiple myeloma’... The data they (Bergsagel *et al.* (15)) present in their Tables 3 and 4 is akin to a fishing expedition in waters known to be sterile”.

5. The industry-sponsored review paper of Paustenbach *et al.* (16) was critically analyzed by Utterback & Rinsky (17) who emphasized the following points:

“Paustenbach *et al.* (16) have apparently overlooked important information in literature related to the use and testing of control ventilation in the rubber hydrochloride (RH) [rubber hydrochloride]

plants even though they extensively cite other information from the very same page of that source”. [p. 665]... and “used selected information, sometimes improperly cited, to adjust previously reported benzene exposure estimates for the RH worker cohort”.

6. Infante (18) critiqued the publication by Sorahan *et al.* (19) as follows:

“In summary, there are inherent data limitations in the Sorahan *et al.* study:

- (i) ‘under-ascertainment’ of cancer deaths;
- (ii) unverifiable benzene exposure for individual cohort members;
- (iii) inadequate attention to analysis by latency; and
- (iv) improper categorization of ANLL. As a result, the study provides little information upon which to evaluate health risks from occupational exposure to benzene”.

7. The Shanghai Health “Study”

In 2005, the petroleum industry proposed a study of benzene in the workplace to be done in Shanghai, China. Dr. Gerhard Raabe was involved in raising money from oil companies for this study. Among senior investigators for this study are Drs. Otto Wong, Richard Irons, and Robert Schnatter. The proposed solicitation for oil company money stated objectives and expected conclusions of the “study” even prior to its beginning. The planned research was expected to provide strong scientific support for the lack of a risk of leukemia or other hematological disease to the general population at current ambient benzene concentrations, establish that adherence to current occupational exposure limits (in the range of 1-5 ppm) does not create a significant risk to workers exposed to benzene, and refute the allegation that Non-Hodgkin’s lymphoma can be induced by benzene exposure.

The Shanghai Health Study is highly reminiscent of tobacco industry’s “preeminent scientists” who testified before a Congressional committee that neither that evidence (1964 Surgeon General’s Report) nor any reported since then suffices to demonstrate that smoking causes any disease.

Ramazzini Foundation Studies

There have been massive efforts by product defense scientists to refute studies published by independent scientists from the RF, Prof. Cesare Maltoni and his associates, Professors Morando Soffritti and Fiorella Belpoggi for the past four decades. Findings of product defense consultants are published in journals that are friendly to industry (20), such as *Regulatory Toxicology & Pharmacology*, *Indoor & Built Environment*, *Journal of Occupational & Environmental Medicine*.

The old adage of “kill the messenger” of bad news is still alive. Industry paid consultants have attacked findings on benzene, formaldehyde, vinyl chloride, MTBE, ETBE, methanol and aspartame conducted by Soffritti and Belpoggi of the RF. The rats and mice of the RF studies have become super stars in their struggle to protect public health.

Criticism of RF Studies

Ward & Alden (21) defend the publication of Shoeb, McConnell, *et al.* (22) criticizing RF studies on MTBE and aspartame. They state, “As professionals in 2009, it behooves us to participate in good science”. The publication, *Veterinary Pathology*, did not identify sponsors of this product-defense paper. However, in the *Conflict of interest statement*, T.R. Schoeb and E.E. McConnell disclose that they were paid consultants of Environ Corp., an environmental consulting firm... E.E. McConnell currently is a study monitor of an industry-supported 2-year drinking water study of MTBE being conducted at the Hamner Institute of Toxicology, Research Triangle Park, NC”.

Environ, a product defense company, is in business to provide money to support findings favorable to industry and suppresses or criticizes those which are not favorable. One can bet that the drinking water “study” is like the Shanghai Study in which results were known before the “study” began.

Schoeb and McConnell (22) contend that the pulmonary lymphomas reported by the RF in studies of aspartame and MTBE were caused by mycoplasma pneumonia infection. Their entire argument gives the appearance of legitimacy is flawed.

These product defense individuals have never visited the inside of RF laboratories and have not seen original slides but are willing to state their opinion. I have visited the RF laboratory more than 150 times and have direct knowledge of their laboratory practices and sound quality control. Schoeb and McConnell have not mentioned collaborative studies between the RF and US governmental scientific agencies and the quality control and blinded studies of slides and data of the RF that have were done by US scientists before any collaboration could be authorized. Schoeb and McConnell did not mention an extensive review of RF studies of chlorinated hydrocarbons was performed in the mid 1980’s. Pathologists from academia, the U.S. EPA, FDA and industry were all in agreement regarding RF data and microscopic characterization of cancers caused by the chemicals under study providing a complete validation and verification of RF data.

In response to Schoeb and McConnell (22) allegations that lymphoblastic lymphomas were due to infections of the lung, several subsequent analyses were performed by Hoel, Soffritti and Belpoggi (submitted for publication). Results clearly demonstrate that, after adjustment for pulmonary infection, there remained a statistically significant dose-response in female rats in the dose range of 400 – 2000 ppm thus disproving the allegations of Shoeb and McConnell.

Even Industry failed to find flaws in the studies of the RF. In 1986, a Mobil management memo (*personal communication*) addresses the scientific quality of RF conduct of long-term carcinogenesis studies. In paragraph #1, the Mobil Management Memo acknowledges that Maltoni found that vinyl chloride, Shell pesticides and other chemicals caused cancers and that rare forms of cancer caused by chemicals in rodents are also found in workers. The memo goes on to say Maltoni would not agree to clear reports of his studies with other industry members, e.g., Shell Oil Corp. Maltoni showed that benzene causes cancers in mouse Zymbal gland. These results were pooh-poohed within API for years because people don’t have Zymbal glands. The U.S. National Toxicology Program and NYU scientists later confirmed his findings. The memo concludes Maltoni “was proven right in every instance [when he defended his results]. We are

confident his scientific work will be accepted as authoritative”.

Starting late in 1979, the RF began to set up, with assistance from Mobil Environmental Health Science Laboratory in the USA, “Good Laboratory Practices”. On February 11, 1982 a quality assurance audit was performed by a group consisting of Prof. Vito Foa of Milan, Antonio Gaddi, Chief Administrator of the Workers’ Union of Milan, Renzo Dal Zotto, administrator of the RF. The Mobil Oil report on March 2, 1982 (*personal communication*) concluded that, “Maltoni is apparently well-known and highly regarded in Italy for his unselfishness, honesty, and devotion to cancer research and his patients. This research laboratory appears to be operated by a high-caliber, dedicated staff consisting mostly of physician pathologists, who are doing exceptionally high quality work”.

Response to more recent critique of RF studies by Caldwell et al. (23)

Goodman *et al.* (24) cite Miller & Nadon (25) on behalf of industry and criticize the use of lifespan studies in RF laboratories. However, US EPA Cancer Guidelines and policy state, “care should be taken to include studies that provide some evidence bearing on carcinogenicity or help interpret effects noted in other studies”... “The unique RF protocol, including lifespan observation... increases the sensitivity of the bioassay in some cases such as lymphoma endpoint”.

It should be noted that the U.S. government under the auspices of the U.S. EPA and FDA, conducted the world’s largest study on a single carcinogen at the U.S. government laboratories National Center for Toxicological Research on 24,172 animals. Some of the animals were exposed for 30 months in order to increase the sensitivity of detection of carcinogenicity (26). The study concluded that, as an official federal regulatory agency policy: “There should be no debate over a key principle that has shaped both our investigations and the regulatory posture of the FDA and EPA namely that no level of exposure to a toxic substance greater than zero can be assumed to be without potentially harmful effects. The evidence from the ED₀₁ study... has provided

massive and overwhelming experimental profiles and the data base lends support to regulatory policies” (26).

Schoeb *et al.* (27, 28) stated that nearly all of the rats at the RF had bronchopneumonia and that the high background incidence of inflammation accounted for the increased incidence of lymphoma/leukemia reported in treated rats was unrelated to aspartame is false. Magnuson & Williams (29) incorrectly stated lung was often the site of the lymphomas. Similar unfounded mischaracterizations were made by industry regarding MTBE, benzene, and other chemicals studied in the RF laboratory over many decades. No study from the 1960’s to date from the RF has been proven invalid. After careful review of RF protocols and slides, there has been no disagreement by governmental scientists with results as reported by the RF. No attempt by industry in the past 40 years has been done to reproduce a single study by using identical protocols. I am certain that any such attempt would yield results similar to those of the RF.

Comparison of studies conducted by the NTP (National Toxicology Program) and the RF

Huff *et al.* (30) listed 14 chemicals that were studied and evaluated by the NTP and the RF. Only three chemicals gave apparently inconsistent results: xylene, vinylidene, and toluene. The differences are readily explainable and do not at all represent inconsistent results. The differences rather are due to length of the studies: two years by National Toxicology Program versus lifetime studies by the RF. NTP and RF results were in agreement on most chemicals. In light of this overwhelming support of quality and studies of the RF, it is difficult to understand the attacks on the RF but not on the NTP by product defense consultants.

References

1. Bailar, JC. How to distort the scientific record without actually lying: truth, and the arts of science. *Eur J Oncol* 2006; 11: 217-24.
2. vom Saal FS, Welshons WV. Large effects from small

- exposures. II. The importance of positive controls in low-dose research on bisphenol A. *Environ Res* 2006; 100: 50-76.
3. Michaels D. Doubt is their product. How industry's assault on science threatens your health. Oxford University Press, 2008.
 4. Fagin D, Lavelle M (Eds). *Toxic Deceptions: How the Chemical Industry Manipulated Science, Bends the Law and Endangers Your Health*. Center for Public Integrity. Birch Lane Press, Carol Pub. Group. Washington, DC, 1999.
 5. Raabe GK, Collingwood KW, Milcarek BI, *et al.* An updated mortality study of workers at the Beaumont, Texas refinery. Dated December 5, 1994. Pages MOB 10229-MOB 10281, 1994.
 6. Infante PF. Benzene and leukemia: Cell types, latency and amount of exposure associated with leukemia. In: Imbriani M, Ghittori S, Pezzagno G, Capodaglio E, Eds. *Update on benzene*. *Advances in Occup Med Rehabil*. Fondazione Salvatore Maugeri Edizioni, Pavia, Italy, 1995; 1: 107-20.
 7. Wong O, Raabe G. Cell type specific leukemia analyses in a combined cohort of more than 208,000 petroleum workers in the U.S. and United Kingdom, 1937-1989. *Reg Toxicol Pharmacol* 1995; 307-21.
 8. Ott MG, Townsend JC, Fishbeck WA, *et al.* Mortality among individuals exposed to benzene. *Arch Environ Health* 1978; 33: 3-10.
 9. Bond GG, McLaren EA, Baldwin CL, *et al.* An update of mortality among workers exposed to benzene. *Br J Ind Med* 1986; 43: 685-91.
 10. Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. II. Dose-response analysis. *Brit J Ind Med* 1987; 44: 382-95.
 11. McMichael AJ. Carcinogenicity of benzene, toluene and xylene: Epidemiological and experimental evidence. *IARC Monographs*. Chapter 1: 1988, 3-18.
 12. Thorpe JJ. Epidemiologic survey of leukemia in persons potentially exposed to benzene. *J Occup Med* 1974; 16: 375-82.
 13. Rushton L, Alderson MR. A case-control study to investigate the association between exposure to benzene and deaths from leukaemia in oil refinery workers. *Br J Cancer* 1981; 43: 77-84.
 14. Goldstein BE, Shalot SL. The causal relation between benzene exposure and multiple myeloma. Letter to the Editor, *Blood* 2000; 95: 1512-3.
 15. Bergsagel DW, Wong O, Bergsagel PL, *et al.* Benzene and multiple myeloma: Appraisal of the scientific evidence. *Blood* 1999; 94: 1174-82.
 16. Paustenbach DJ, Price PS, Ollison W, *et al.* Reevaluation of benzene exposure for the Pliofilm (rubber-worker) Cohort, (1936-1976). *J Toxicol Environ Health* 1992; 36: 177-231.
 17. Utterback DF, Rinsky RA. Benzene exposure assessment in rubber hydrochloride workers: A critical evaluation of previous estimates. *Am J Ind Med* 1995; 27: 661-76.
 18. Infante PF. The past suppression of industry knowledge of the toxicity of benzene to humans and potential bias in future benzene research. *Int J Occup Environ Health* 2006; 12: 268-72.
 19. Sorahan T, Kinlen LJ, Doll R. Cancer risks in an historical UK cohort of benzene exposed workers. *Occup Environ Med* 2005; 62: 231-6.
 20. Michaels D. Manufactured uncertainty. Protecting public health in the age of contested science and product defense. *Ann NY Acad Sci* 2006; 1076: 149-62.
 21. Ward JM, Alden CL. Confidence in rodent carcinogenesis bioassays. *Vet Pathol* 2009; 46: 790-1.
 22. Caldwell JC, Jinot J, Devoney D, *et al.* Response to Letters to the Editor: Caldwell *et al.* (2008). *Envir Molec Mutagen* 2009; 50: 6-9.
 23. Goodman JE, Gaylor D, Beyer LA. Effects of MTBE on the reported incidence of Leydig cell tumors in Sprague-Dawley rats: Range of possible Poly-3 results. *Reg Toxicol Pharmacol* 2008; 50: 273-84.
 24. Schoeb TR, McConnell EE, Juliana MM, *et al.* *Mycoplasma pulmonis* and lymphoma in bioassays in rats. *Vet Pathol* 2009; 46: 952-9.
 25. Miller RA, Nadon DL. Principles of animal use for gerontological research. *J Gerontol Biol Sci Med Sci* 2000; 55: B117-B118.
 26. Staffa JA, Mehlman MA. *Innovations in Cancer Risk Assessment (ED₀₁ Study)*. Pathotox Publishers, Inc., Park Forrest, IL, 1979.
 27. Schoeb TR, Juliana MM, Nichols PW, *et al.* Effects of viral and mycoplasmal infections, amonia exposure, vitamin A deficiency, host age, and organism strain on adherence of *Mycoplasma pulmonis* in cultured rat trachea. *Lab Anim Sci* 1993; 43: 417-24.
 28. Schoeb TR. Respiratory diseases of rodents. *Vet Clin North Am* 2000; 3: 481-96.
 29. Magnuson G, Williams GM. Letter to the editor. *Environ Health Perspect* 2008; 116: A239-A240.
 30. Huff J. Chemicals studied and evaluated in long-term carcinogenesis bioassays by both the Ramazzini Foundation and the National Toxicology Program: in tribute to Cesare Maltoni and David Rall. *Ann NY Acad Sci* 2003; 982: 208-30.

