

# FUELS: A PERSISTENT THREAT TO PUBLIC HEALTH

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**Ramazzini Lecture**

**27 October 2007**

*In the tradition of Bernardino Ramazzini*

*To honor the memory of Cesare Maltoni*



## Motor vehicle use (thousands) (a)

| Country or Area      | Motor vehicles in use | 1980           | 2003           | 2004          |
|----------------------|-----------------------|----------------|----------------|---------------|
| <b>China</b>         | Passenger cars        | <b>351</b>     | 14,788         | <b>17,359</b> |
| China                | Commercial vehicles   | 1,299          | 8,535          | 8,930         |
| Germany              | Passenger cars        | 23,192         | 44,657         | 45,023        |
| Germany              | Commercial vehicles   |                | 3,551          | 3,505         |
| <b>India</b>         | Passenger cars        | <b>1,059</b>   | <b>8,619</b>   |               |
| India                | Commercial vehicles   | 1,345          | 10,889         |               |
| Italy                | Passenger cars        | 17,000         | 34,310         | 33,973        |
| Italy                | Commercial vehicles   | 1,000          | 3,934          | 4,016         |
| <b>United States</b> | Passenger cars        | <b>170,543</b> | <b>222,701</b> |               |
| United States        | Commercial vehicles   | 6,590          | 8,689          |               |

(a) United Nations Statistical Yearbook 2007

## Projected growth of Chinese car market

**“The Chinese car market, now the third-largest in the world, is expected to continue growing at about 15 per cent a year, with demand reaching 9m cars a year by the end of the decade. Yet at present only about 1.25 per cent of the population possesses a car. If car ownership reached the levels of the US, China would have more than 1 billion vehicles.”**

*Financial Times, January 27, 2006*

# ERF integrated project on fuels:

## FUEL MIXTURES

| Compound Tested                       | n.<br>bioassays | species  | n. animals  | carcinogenicity | year of<br>publication |
|---------------------------------------|-----------------|----------|-------------|-----------------|------------------------|
| Unleaded gasoline                     | 2               | S-D rats | 540         | +               | 1997                   |
| Leaded gasoline                       | 1               | S-D rats | 300         | +               | 1997                   |
| Gasoline containing 3% methyl alcohol | 1               | S-D rats | 240         | ongoing         |                        |
| Gasoline containing 5% ethyl alcohol  | 1               | S-D rats | 240         | ongoing         |                        |
| Gasoline containing 15% MTBE          | 1               | S-D rats | 240         | +               |                        |
| Gasoline containing 15% ETBE          | 1               | S-D rats | 240         | (+)             |                        |
| Kerosene                              | 1               | S-D rats | 300         | +               | 1997                   |
| Diesel fuel                           | 1               | S-D rats | 300         | +               | 1997                   |
| <b>Total</b>                          | <b>9</b>        |          | <b>2400</b> |                 |                        |

## ERF integrated project on fuels:

### MAJOR AROMATIC HYDROCARBON CONSTITUTENTS

| Compound Tested  | n.<br>bioassays | species  | n. animals  | carcinogenicity | year of<br>publication |
|------------------|-----------------|--|-------------|-----------------|------------------------|
| Benzene          | 8               | S-D rats, Wistar<br>rats, Swiss mice,<br>RF/J mice | 1950        | +               | 1977                   |
| Toluene          | 4               | S-D rats   | 440         | +               | 1997                   |
| Xylenes          | 2               | S-D rats   | 380         | +               | 1997                   |
| Ethylbenzene     | 2               | S-D rats   | 380         | +               | 1997                   |
| Trimethylbenzene | 2               | S-D rats   | 408         | +               | 1997                   |
| <b>Total</b>     | <b>18</b>       |  | <b>3558</b> |                 |                        |

## ERF integrated project on fuels:

### OXYGENATED ADDITIVES

| Compound Tested                   | n.<br>bioassays | species                 | n. animals  | carcinogenicity | year of<br>publication |
|-----------------------------------|-----------------|-------------------------|-------------|-----------------|------------------------|
| Methyl alcohol                    | 3               | S-D rats                | 1340        | +               | 2002                   |
| Ethyl alcohol                     | 4               | S-D rats, Swiss<br>mice | 1458        | +               | 2002                   |
| Methyl-tert-butyl ether<br>(MTBE) | 1               | S-D rats                | 360         | +               | 1995                   |
| Ethyl-tert-butyl ether<br>(ETBE)  | 1               | S-D rats                | 360         | (+)             | 1999                   |
| Ter-amyl-methyl ether<br>(TAME)   | 1               | S-D rats                | 600         | +               | 2002                   |
| Di-isopropyl ether<br>(DIPE)      | 1               | S-D rats                | 600         | +               | 2002                   |
| <b>Total</b>                      | <b>11</b>       |                         | <b>4718</b> |                 |                        |

## ERF integrated project on fuels:

### ISOPARAFFINS

| Compound Tested        | n.<br>bioassays | species  | n. animals | carcinogenicity | year of<br>publication |
|------------------------|-----------------|----------|------------|-----------------|------------------------|
| 2,2,4-trimethylpentane | 2               | S-D rats | 408        | -               |                        |
| <b>Total</b>           | <b>2</b>        |          | <b>408</b> |                 |                        |

# ERF integrated project on fuels:

## COMBUSTION PRODUCTS

| Compound Tested | n.<br>bioassays | species  | n. animals  | carcinogenicity | year of<br>publication |
|-----------------|-----------------|----------|-------------|-----------------|------------------------|
| Acetaldehyde    | 4               | S-D rats | 870         | +               | 2002                   |
| Formaldehyde    | 4               | S-D rats | 1447        | +               | 1989                   |
| <b>Total</b>    | <b>4</b>        |          | <b>1447</b> |                 |                        |



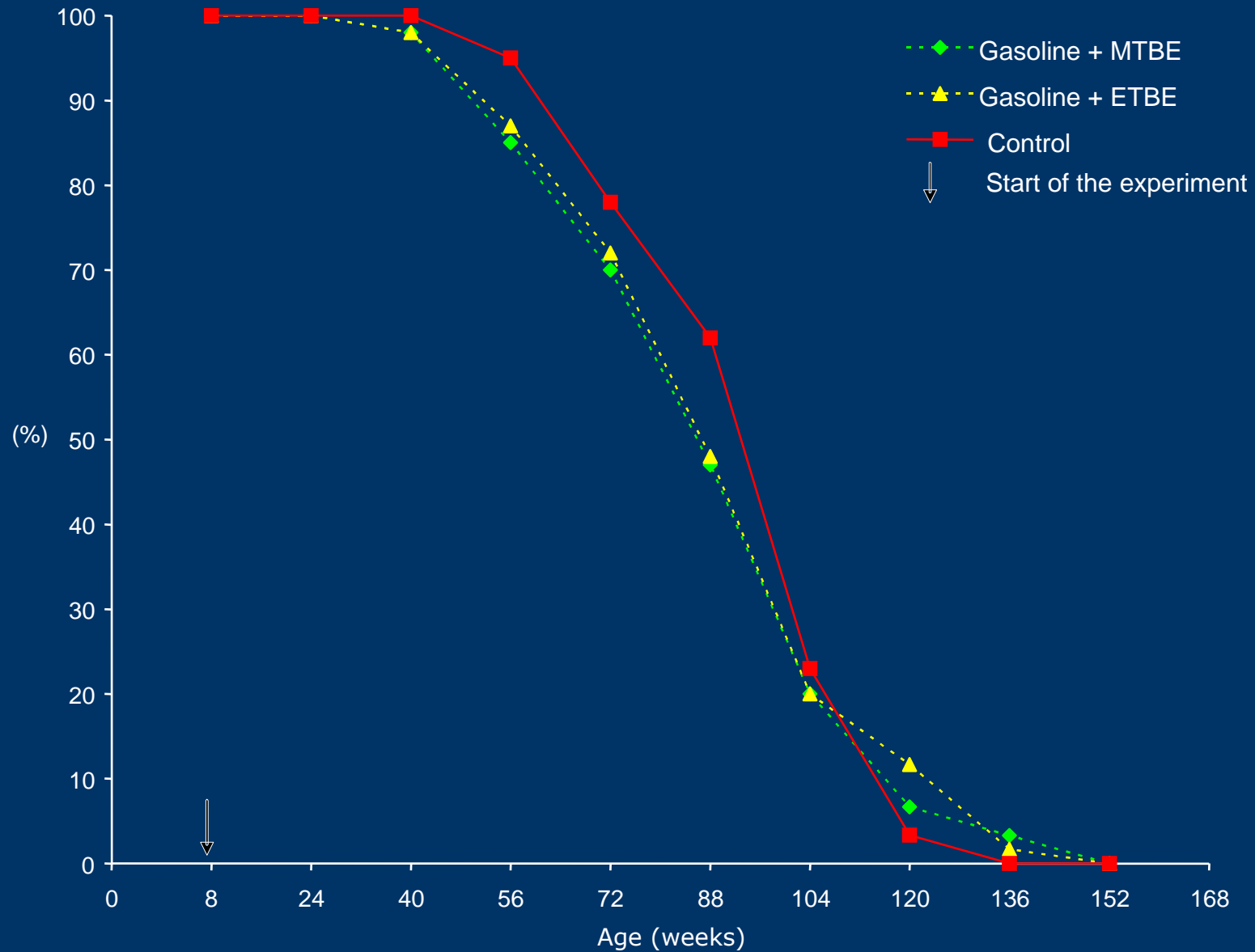
# Gasoline mixtures (BT962): plan of the experiment

Long-term carcinogenicity bioassay on gasoline containing oxygenated additives, METHYL-TERTIARY-BUTYL ETHER (MTBE) or ETHYL-TERTIARY-BUTYL ETHER (ETBE), administered by stomach tube to male (M) and female (F) Sprague-Dawley rats

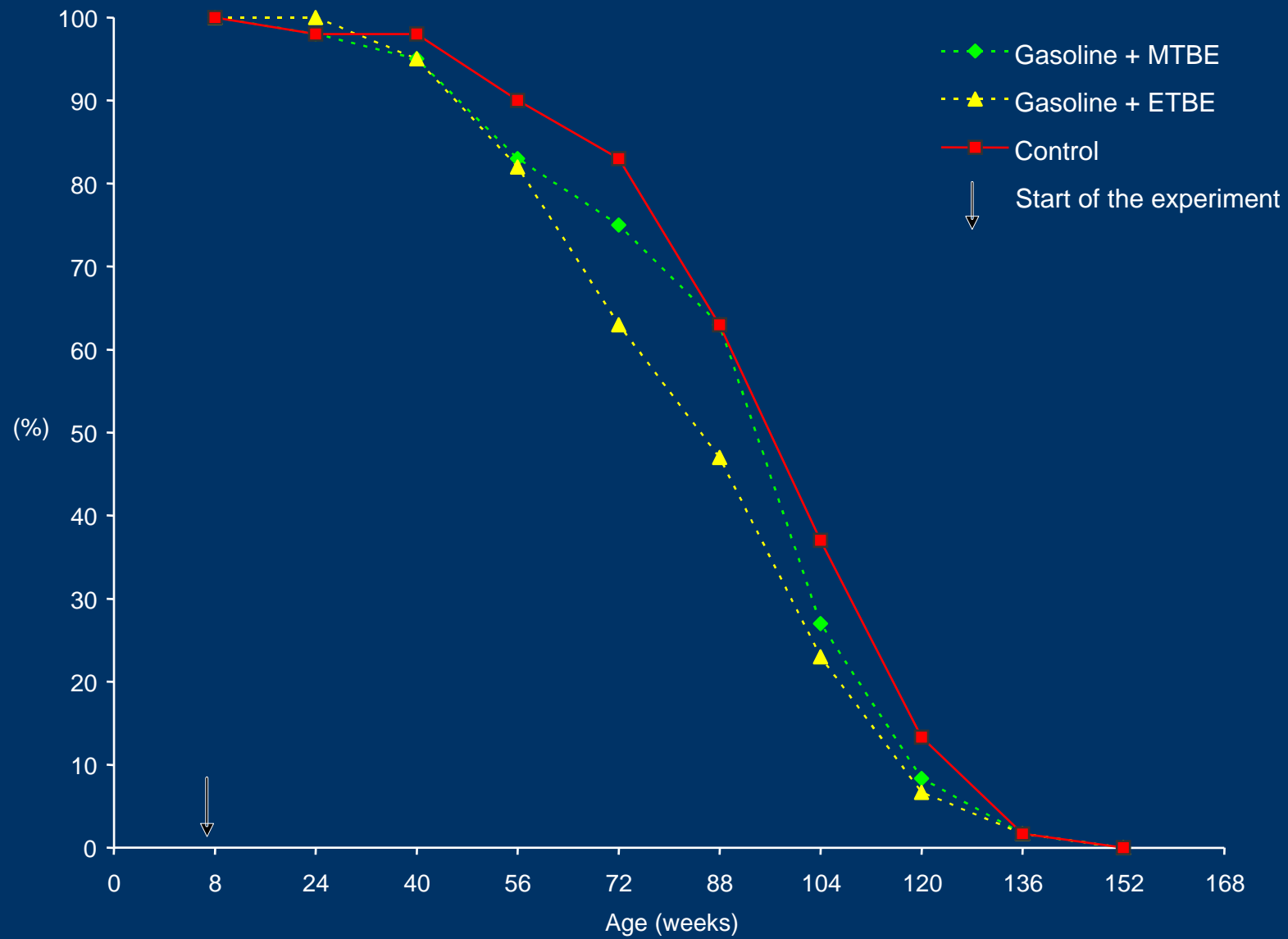
| Groups No. | Treatment <sup>a</sup>             |                      | Animals              |     |     |
|------------|------------------------------------|----------------------|----------------------|-----|-----|
|            | Gasoline (mg/kg b.w. In olive oil) | Oxygenated additives | Age at start (weeks) | Sex | No. |
| I          | 800                                | MTBE 15%             | 8                    | M   | 60  |
|            |                                    |                      |                      | F   | 60  |
|            |                                    |                      |                      | M+F | 120 |
| II         | 800                                | ETBE 15%             | 8                    | M   | 60  |
|            |                                    |                      |                      | F   | 60  |
|            |                                    |                      |                      | M+F | 120 |
| III        | 0 (control) olive oil alone        | -                    | 8                    | M   | 60  |
|            |                                    |                      |                      | F   | 60  |
|            |                                    |                      |                      | M+F | 120 |

<sup>a</sup> Duration for 104 weeks

# Gasoline mixtures (BT962): survival males



# Gasoline mixtures (BT962): survival females



# Gasoline mixtures: summary results

## Tumor Bearing Animals (%)<sup>(a)</sup>

| Tumors                 | Sex | Total benign | Total malignant | Mammary gland fibroadenomas | Head osteosarcomas | Pituitary gland adenomas | Adrenal gland pheochromo | HLRN        |
|------------------------|-----|--------------|-----------------|-----------------------------|--------------------|--------------------------|--------------------------|-------------|
| Gasoline with 15% MTBE | M   | <b>55.0</b>  | -               | -                           | -                  | -                        | -                        | -           |
|                        | F   | -            | -               | <b>41.7</b>                 | -                  | -                        | <b>15.0</b>              | <b>25.0</b> |
| Gasoline with 15% ETBE | M   | -            | -               | -                           | -                  | <b>30.0</b>              | -                        | -           |
|                        | F   | -            | <b>51.7</b>     | <b>36.7</b>                 | <b>13.3</b>        | -                        | -                        | -           |
| Control                | M   | 45.0         | -               | -                           | -                  | 16.7                     | 6.7                      | -           |
|                        | F   | -            | 43.3            | 33.3                        | 3.3                | -                        | -                        | 11.7        |

(a) only incidence with significant increase ( $p \leq 0.05$ ) are reported

## State of the art on fuels research in 1995

1) "Our data indicate the carcinogenic risk of gasoline, of some of its components, including additives, and of some of its exhausts. Since several of the agents studied turned out to be carcinogenic, from the public health angle, one must consider possible syncarcinogenic effects. Besides the information they afford, our data show the need for further studies to define and quantify the carcinogenic risk of gasoline."

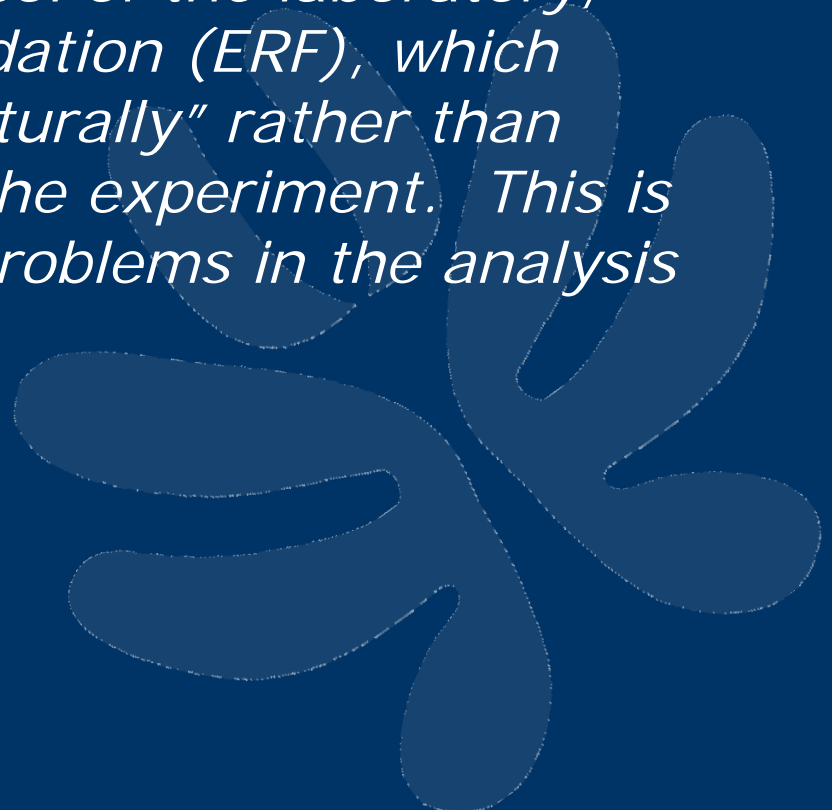
2) "[Our studies] also stress the requirement that all new modifications to gasoline composition be submitted to appropriate biomedical research to screen them from potential risks, or at least reduce the risks, before they go into production."

- Cesare Maltoni, Ramazzini Lecture 1995

## Criticism 1

### USE OF LIFESPAN EXPERIMENTAL PROTOCOL


*“the lifetime study [on MTBE] was conducted according to the normal protocol of the laboratory, the European Ramazzini Foundation (ERF), which permits the rodents to die “naturally” rather than imposing a finite duration on the experiment. This is very unusual and introduces problems in the analysis of data.”*



## Criticism 2

### DIAGNOSTIC CRITERIA OF PATHOLOGICAL LESIONS

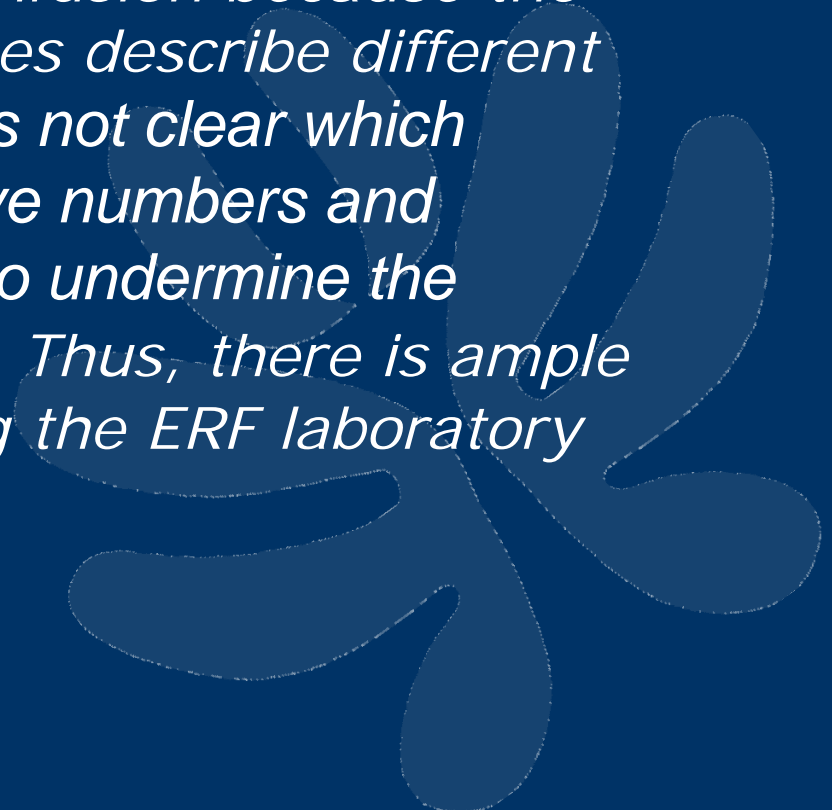
*“on one of the rare occasions when microscopic slides from a ERF study have been made available for independent review...the conclusion reached by the Pathology Working Group was that the ERF study pathologists appeared to apply more severe classifications than the NTP pathologists.”*



## Criticism 3

### MULTIPLE PUBLICATIONS OF EXPERIMENTAL DATA

*“the ERF practice of providing multiple publications of the same study can lead to confusion because the different publications sometimes describe different results. When this happens, it is not clear which publication contains the definitive numbers and diagnosis, a feature that tends to undermine the confidence of the data reported. Thus, there is ample basis for uncertainty regarding the ERF laboratory experiments in general.”*

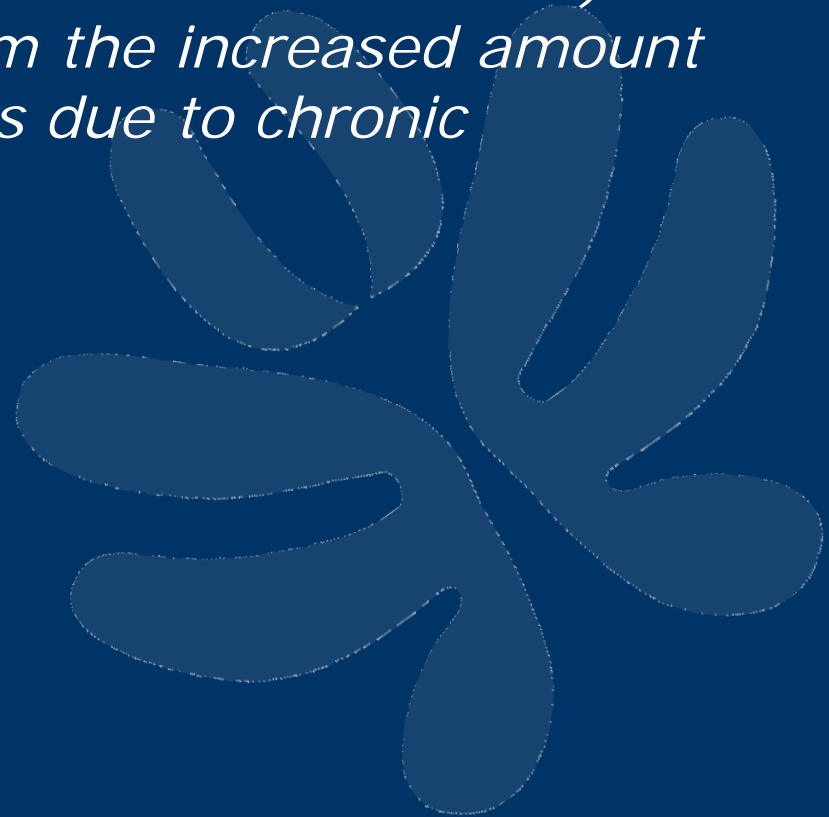




## Criticism 4

### CHRONIC PULMONARY INFLAMMATION IN OUR RODENT COLONY

*"...such neoplasms (i.e. lymphomas and leukemia) have been known to arise from the increased amount of lymphoid tissue in the lungs due to chronic pulmonary inflammation."*



## Criticism 5

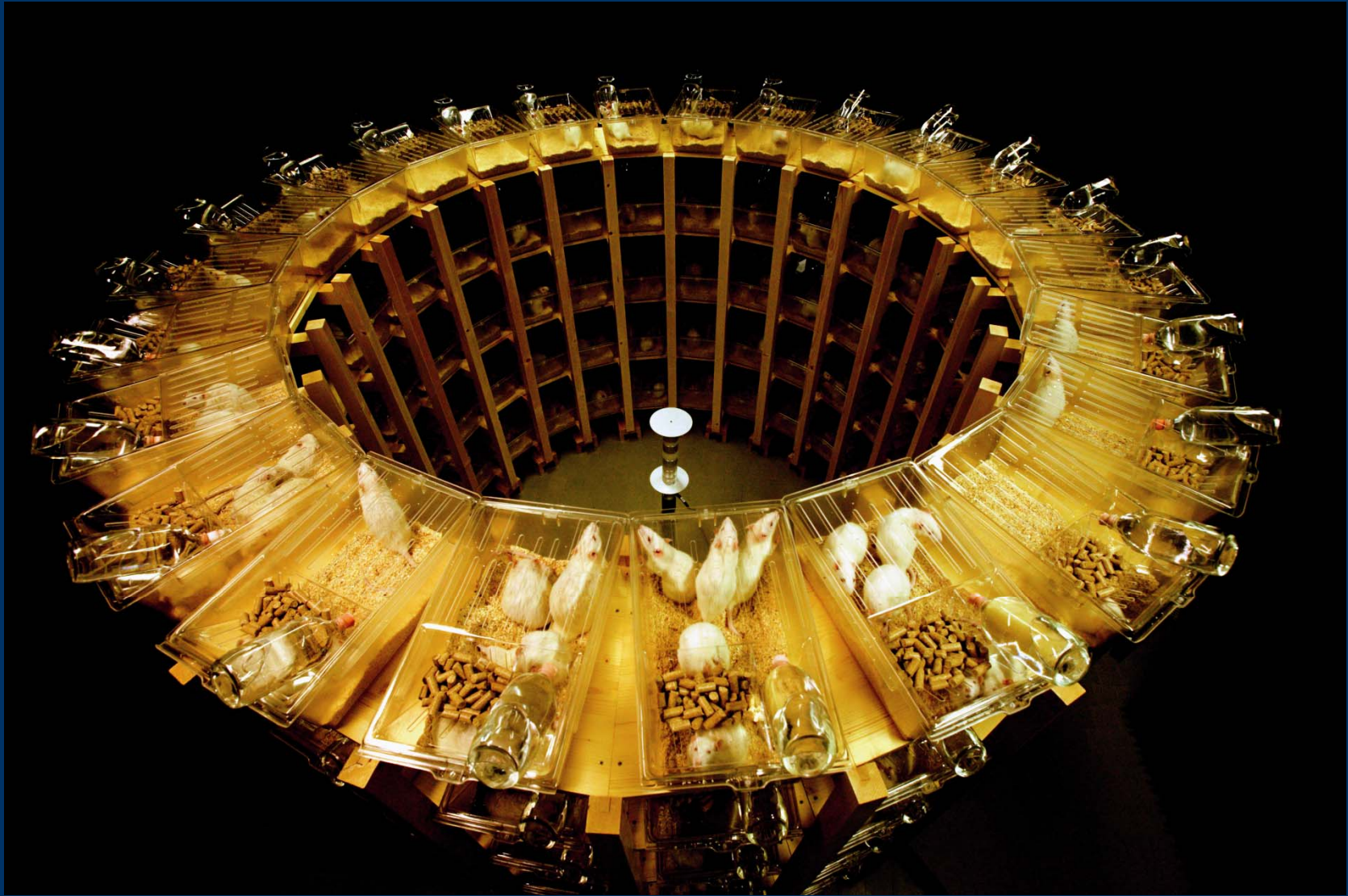
NO ONE REALLY KNOWS JUST WHAT THOSE  
ITALIANS DO IN THAT CASTLE ANYWAY


























## Criticism 5

### NO ONE REALLY KNOWS JUST WHAT THOSE ITALIANS DO IN THAT CASTLE ANYWAY

*“the [Ramazzini] laboratory is reluctant to submit to a proper and throughout review. The ERF has always resisted these cooperative practices, consequently generating suspicion and earning a reputation for secrecy.*



## Industry site visit to Ramazzini laboratories

**“Maltoni is apparently well-known and highly respected in Italy for his unselfishness, honesty and devotion to cancer research and to his patients. His research laboratory appears to be operated by a high-caliber, dedicated staff (mostly M.D. pathologists) who are doing exceptionally high quality work.”**

*- Report of the Mobil Corporation, 1982*



## International reputation of Ramazzini laboratories

**"I want to say this as strongly as I possibly can. Cesare Maltoni is one of the most distinguished scientists in the history of toxicology in the world. There is no finer toxicologist anywhere than Cesare Maltoni...I think we have to take this [MTBE] study very seriously, both in terms of the quality of the study, the response to the questions and third, the history of the man"**

*Dr. John Froines before the California Environmental Protection Agency, 1999*

## Belief vs. Scientific Truth

**“Those who are able to reason and have the will to apply themselves, are able to repeat the same experience to verify the results.”**

- Founding fathers of modern science, Galileo, Descartes, and Pascal




## State of the art on fuels research in 1995

1) "Our data indicate the carcinogenic risk of gasoline, of some of its components, including additives, and of some of its exhausts. Since several of the agents studied turned out to be carcinogenic, from the public health angle, one must consider possible syncarcinogenic effects. Besides the information they afford, our data show the need for further studies to define and quantify the carcinogenic risk of gasoline."

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## Production and use of biodiesel

- By the end of 2005 industry production of corn grain ethanol and soybean biodiesel was 75 million gallons - a 300% increase in 1 year.
  - Biodiesel content in diesel fuel is required by law in some US states.
  - 21 European countries have commercial biofuels projects.
- 

## Long-term health effects of biodiesel

The exhausts of biodiesel fuels are aggregated toxics, i.e. aldehydes, acrolein, benzene, 1-3 butadiene, ethylbenzene, n-hexane, naphthalene, styrene, toluene, and xylene.

- Draft technical report of the US EPA, 2002





## Conclusions from 1995 and today

“To promote the growth of biomedical research into development research, and its indisputable roles in the decision-making that shapes the trends of development itself, is actual fact, the prime reason why the **Collegium Ramazzini** came into being.”

- Cesare Maltoni, Ramazzini Lecture 1995



# Per aspera ad astra

One only arrives at the stars by overcoming  
great difficulty

*-Seneca*

