Virchows Arch. A Path. Anat. and Histol. 371, 131—143 (1976)


# Investigations into Human Thorotrastosis*

## Tissue Concentrations of 232-Th and Late Effects in 13 Autopsy Cases

K. Wegener, H. Wesch, and H. Kampmann

Institute of Pathology, Municipal Hospitals of Ludwigshafen a. Rhein (Prof. K. Wegener), Institute of Nuclear Medicine, German Cancer Research Institute, Heidelberg (Prof. K. Scheer), and Institute of Pathology, University of Heidelberg (Prof. W. Doerr)

Received January 30, 1976

*Summary.* The subjects of investigation were 13 dead thorotrast patients, 10 male, 3 female, with ages ranging from 45 to 79 years. Two thousand organ and tissue specimens were investigated by means of autopsy and by both microscopic-autoradiographic and neutron activation analysis in order to detect late effects and to determine on approximate mean concentration of $^{232}Th$ (mg per g of tissue).

A comparison between late effects and concentrations of the dye medium led to the following conclusions:

1. $^{232}Th$ is, after intravascular injection, deposited in *all organs and tissues* of the human body.
2. The highest mean concentrations are shown in the spleen, liver, bone marrow, and lymph nodes.
3. The distribution of $^{232}Th$ is inhomogeneous in all organs and tissues. The variations of maximum and minimum concentration lie around factor $2.2\times10^{0}$–$2.4\times10^{5}$.
4. Late effects occur only in spleen, liver, lymph nodes, and bone marrow, but not in organs and tissues that show a mean concentration of $^{232}Th$ under $10^{-1}$ mg per g tissue.
5. It is highly probable that tumors of thorotrast patients in organs other than spleen, liver, lymph nodes, and bone marrow are not caused by deposition of $^{232}Th$ or $ThO_2$.

*Zusammenfassung.* Bei 13 verstorbenen Thorotrastpatienten (10 Männern und 3 Frauen) im Alter zwischen 45 und 79 Jahren sind durch Obduktion, mikroskopisch-autoradiographische Untersuchungen und Neutronen-Aktivierungsanalyse von ca. 2000 Organ- und Gewebsproben die makroskopisch und mikroskopisch erkennbaren Spätschäden sowie angenäherte mittlere Konzentrationen (Medianwerte) von $^{232}Th$ (mg/g Gewebe) festgestellt worden.

Eine Gegenüberstellung von Spätschäden und Konzentrationen des Kontrastmittels erlaubte folgende Feststellungen:

1. $^{232}Th$ wird in *allen Organen und Geweben* des menschlichen Körpers nach intravasaler Applikation abgelagert.
2. Die höchsten mittleren Konzentrationen weisen Milz, Leber, Knochenmark und Lymphknoten auf.
3. $^{232}Th$ ist in allen Organen und Geweben inhomogen verteilt mit Schwankungen von maximaler und minimaler Konzentration um den Faktor $2{,}2\times10^{0}$—$2{,}4\times10^{5}$.
4. Spätschäden treten nur auf in Milz, Leber, Lymphknoten und Knochenmark, nicht aber in Organen und Geweben mit einer mittleren Konzentration an $^{232}Th$ unter $10^{-1}$ mg/g Gewebe.
5. Tumoren bei Thorotrastpatienten in anderen Organen als in Milz, Leber, Lymphknoten und Knochenmark sind mit hoher Wahrscheinlichkeit nicht Folge der Ablagerungen von $^{232}Th$ bzw. $ThO_2$.

* Dedicated to Prof. Dr. W. Maurer on his 70th birthday.

## A. Introduction

The contrast medium, thorotrast, because of its cancerogenic effects, has not been used for the past 20–25 years. Consequently, in a few years time, there will be no thorotrast patients left. In spite of this, findings in the field of human thorotrastosis are, for several reasons, still of interest:

1. As time goes by, an ever-increasing number of people will be exposed to radiation as a direct result of their contact with radionuclides in industrialized areas. Up to now, there is insufficient data which refers to the distribution of such nuclides in the human body. Investigation, both qualitative and quantitative, into living and dead thorotrast patients, could lead to the discovery of important information. Of particular importance will be those cases where, in spite of deposits of radioactive foreign bodies, late effects did not occur.

2. So far, it is not clear whether tumors in general thorotrastosis are caused by ionizing radiation alone, or by the stimulus of foreign bodies, or, indeed, by both factors together It is also not clear which organ-specific factors are responsible for the very different frequency of tumors in certain organs, in spite of an equal concentration of radioactivity. All these are questions which have become topical in recent years because of findings made in industrial pathology and which can only be given partial solutions by recourse to animal experiments. (Wenz, 1964; Benstedt, 1967; Riedel et al., 1973.)

3. In some cases of the so-called PVC-disease, hämangioendotheliosarcomas of the liver have been observed. These tumors very seldom occur spontaneously in this organ but they are very frequent in patients suffering from thorotrastosis (Lüdin, 1953; Frühling et al., 1955; Grampa and Degna, 1958; Silva Horta et al., 1965; Hohenstatt, 1965; Kemnitz, 1964; Barousch, 1969; Wegener and Zahnert, 1970; Hofbauer and Häring, 1970; Wegener et al., 1971; van Kaick and Scheer, 1973; Edit, 1974; Edit, 1974; Lange et al., 1974; Lee and Harry, 1974; Roe, 1974; Futh and Pietzke, 1975.)

This raises the question whether the development of this type of tumor can reveal something about the way in which such different substances as thorotrast and PVC (or its subunits) work.

In the course of our pathologic-anatomic investigations into the late effects of human thorotrastosis, we had determined the quantity of $^{232}Th$ by means of neutron activation analysis and then began our initial synopsis of the pathology and distribution pattern (Kampmann et al., 1969; Wegener and Zahnert, 1970; Wegener et al., 1969, 1970, 1972, 1973; Wesch et al., 1973). Since then, the research material has grown to 2000 specimens taken from 13 autopsy cases, and we can try to answer the following questions using qualitative and quantitative data:

1. Where exactly is $^{232}Th$ in the form of $ThO_2$ deposited after intravascular injection of thorotrast?

2. Which concentrations of $^{232}Th$ are found in various organs and tissues?

3. Is the distribution of $^{232}Th$ in organs and tissues homogeneous or inhomogeneous?

4. Is there relationship between the concentration of $^{232}Th$ in an organ and the onset of late effects?

## B. Material and Methods

Altogether, we examined 2019 organ and tissue specimens of 13 autopsy cases in order to ascertain the quantity of $^{232}Th$. All 13 patients had received intra-arterial injections of thorotrast 25–30 years previously. The quantity injected and the age of the solution were, in most cases, not known. We took organ specimens for control investigations from current autopsy material. After weighing the organ specimens we determined the quantities of $^{232}Th$ by using neutron activation analysis (Edgington, 1967; Scheer et al., 1967; Kampmann et al., 1968;

Kaul and Heyder, 1968; Wesch et al., 1973). For this process, we freeze-dried the tissue specimens which weighed about 0.5–2.0 g each. Then 32 samples, together with 8 standards, which contained different but known concentrations of thorium, were irradiated in the rotating position of the research reactor Triga Mark I of the German Cancer Research Center. The flux during the irradiation was $2.10^{12}\,n \cdot s^{-1} \cdot cm^{-2}$. The irradiation time lasted about 8 h. The nuclear reaction equation for the irradiation and the decay of the thorium is as follows:

$$^{232}\text{Th}\ (n, \gamma) \rightarrow {}^{233}\text{Th} \xrightarrow[22\ m]{\beta^-} {}^{233}\text{Pa} \xrightarrow[27\ d]{\beta^-} {}^{233}\text{U}.$$

The neutron capture of thorium 232 causes the conversion to thorium 233, which decays with a half-life of 22 min to protactinium 233. This decays with a half-life of 27 days to uranium 233. This long half-life permits the activities of elements like sodium, bromine, chlorine, etc. to decay. They were also produced by neutron irradiation and disturbed the detection of thorium. The rule is, that the quantitative measurements were done 14 days after the end of the irradiation. For this purpose the $\gamma$-rays, which resulted in the decay of protactinium, were measured. By integration of the photopeak of the standard it is possible to determine the content of thorium in the sample. The measurements were done by a Germanium Lithium drifted detector or a $5'' \times 5''$ Na-J well type detector, depending on the content of thorium in the sample. The limit of detection without chemical separation amounts to about 0.1–0.05 µg, depending on the phosphorus content in the sample. The margin error for this method is about 5%. When referring to deposits of $^{232}$Th in the following pages, we always mean the deposition in $ThO_2$ form.

## C. Results

Table 1 shows the data about sex and age of the patients at the time of death, site of thorotrast injection, duration of effect of $^{232}$Th, primary disease at the time of hospital admission, and cause of death.

We investigated tissue specimens of 10 males and 3 females, their ages ranging between 45 and 79 years. All of them had received intra-arterially an unknown quantity of thorotrast 22–30 years before death. Eight patients died in a coma hepaticum, 3 of cachexia combined with bronchopneumonia, and 2 of cardiac and renal insufficiency. In those cases where thorotrastosis was mentioned, morphologically defined organ changes could not be determined during the short hospital stay.

Table 2 shows macroscopically and microscopically diagnosed late effects in the organs of the RES. Ten patients developed carcinomas and hepatic sarcomas in cirrhosis of the liver; in one case we found liver cirrhosis only, in another only a fibrosis of the liver. In all cases, the spleen showed fibrosis and atrophy in varying degrees. In patient No. 3 the spleen was extirpated years before death. In one case only (No. 7) we found a benign hemangioendothelioma of the spleen. The lymph nodes revealed, depending on their position and the amount of $^{232}$Th stored, various degrees of fibrosis with atrophy of the lymphatic tissue. In none of the cases did we observe late effects such as leukemia or malignant lymphoma. There are also references in the table, unspecified for each case, of changes in the bone marrow, but these will be dealt with in a later paper, referring to the quantitative sedimentation of various degrees of $^{232}$Th in bones. We saw some cases with activation as well as depression of the blood production, but also cases without morphologic changes. There was no incidence of leukemia, reticulum cell sarcomas, Ewing's sarcomas, or other malignant processes.

Table 1. Injection data and clinical data of the 13 patients

| Case | Sex | Age at death (years) | Site of injection | Duration of effect | Primary disease | Cause of death |
|---|---|---|---|---|---|---|
| 1 | male | 59 | A.subcl. | 25 | hypertension | cardiac insufficiency |
| 2 | male | 72 | A.carot.comm. | 27 | liver cirrhosis | bronchopneumonia |
| 3 | male | 56 | A.carot.comm. | 27 | liver cirrhosis | coma hepaticum |
| 4 | male | 51 | A.carot.comm. | 28 | thorotrastosis | renal insufficiency |
| 5 | male | 65 | A.femor. | 26 | thorotrastosis | coma hepaticum |
| 6 | female | 56 | A.carot.comm. | 30 | thorotrastosis | coma hepaticum |
| 7 | female | 45 | A.femor. | ca. 28 | thorotrastosis | coma hepaticum |
| 8 | female | 72 | A.carot.comm. | ca. 22 | stomach cancer | coma hepaticum |
| 9 | male | 53 | A.radialis | 28 | thorotrastosis | coma hepaticum |
| 10 | male | 55 | A.femor. | 26 | hepatic cancer | coma hepaticum |
| 11 | male | 53 | A.carot.comm. | 27 | hepatic cancer | coma hepaticum |
| 12 | male | 79 | unknown | unknown | liver cirrhosis | bronchopneumonia |
| 13 | male | 53 | A.femor. | 29 | thorotrastosis | cachexia |

Table 2. Table of the late effects in organs of the RES

| Case | Liver | Spleen | Lymph nodes | Bone marrow |
|---|---|---|---|---|
| 1 | cirrhosis | fibrosis and atrophy | fibrosis | |
| 2 | cirrhosis | fibrosis and atrophy | | |
| 3 | cirrhosis; bile duct carcinoma | | fibrosis | |
| 4 | cirrhosis; bile duct carcinoma | fibrosis and atrophy | | |
| 5 | cirrhosis; hemangioendothelial sarcoma | fibrosis and atrophy | | |
| 6 | cirrhosis; hemangioendothelial sarcoma | fibrosis and atrophy | | activation; depression; |
| 7 | cirrhosis; hemangioendothelial sarcoma | fibrosis; hemangioendothelioma | | without morphologic |
| 8 | cirrhosis; liver cell carcinoma | fibrosis and atrophy | fibrosis | changes |
| 9 | cirrhosis; hemangioendothelial sarcoma | fibrosis | fibrosis | |
| 10 | cirrhosis; hemangioendothelial sarcoma | fibrosis and atrophy | fibrosis | |
| 11 | cirrhosis; bile duct carcinoma | fibrosis and atrophy | fibrosis | |
| 12 | cirrhosis | fibrosis | | |
| 13 | fibrosis | fibrosis and atrophy | fibrosis | |

Table 3. Group I: Organs and tissues with a median value $m \geqq 10^{\circ}$ mg $^{232}$ Th/g tissue

| Organ/Tissue | $n$ | $m$ (mg/g) | $c_{min}$–$c_{max}$ (mg/g) | $Q = \frac{c_{max}}{c_{min}}$ |
|---|---|---|---|---|
| lymph nodes (axis: liver-spleen) | 19 | $68.4 \cdot 10^{0}$ | $2.5 \cdot 10^{0}$ –$9.9 \cdot 10^{1}$ | $4.0 \cdot 10^{1}$ |
| spleen | 14 | $12.7 \cdot 10^{0}$ | $9.0 \cdot 10^{-3}$–$2.1 \cdot 10^{2}$ | $2.3 \cdot 10^{4}$ |
| liver | 959 | $4.1 \cdot 10^{0}$ | $8.0 \cdot 10^{-3}$–$1.8 \cdot 10^{2}$ | $2.3 \cdot 10^{4}$ |
| lymph nodes (A.renalis) | 11 | $7.9 \cdot 10^{0}$ | $3.4 \cdot 10^{-2}$–$6.9 \cdot 10^{1}$ | $2.0 \cdot 10^{3}$ |

Section 1: Investigated organ or tissue
Section 2: Number ($n$) of examined specimens
Section 3: Median value ($m$) of concentrations of $^{232}$ Th in mg per g tissue
Section 4: Smallest ($c_{min}$) and greatest ($c_{max}$) concentration of $^{232}$ Th in a sample in mg per g tissue
Section 5: Ratio of greatest to smallest concentration ($Q = c_{max}/c_{min}$)

Table 4. Group II: Organs and tissues with a median value $10^{\circ} > m \geqq 10^{-1}$ mg $^{232}$ Th/g tissue

| Organ/Tissue | $n$ | $m$ (mg/g) | $c_{min}$–$c_{max}$ (mg/g) | $Q = \frac{c_{max}}{c_{min}}$ |
|---|---|---|---|---|
| lymph nodes (inguinal flexure) | 6 | $3.3 \cdot 10^{-1}$ | $5.6 \cdot 10^{-2}$—$3.8 \cdot 10^{-1}$ | $6.8 \cdot 10^{0}$ |
| lymph nodes (hilum and bronchus) | 30 | $2.5 \cdot 10^{-1}$ | $2.0 \cdot 10^{-2}$—$6.9 \cdot 10^{0}$ | $3.5 \cdot 10^{2}$ |
| tonsils | 11 | $2.0 \cdot 10^{-1}$ | $7.0 \cdot 10^{-5}$—$5.5 \cdot 10^{-1}$ | $7.9 \cdot 10^{3}$ |
| lymph nodes (bifurcatio aortae) | 9 | $1.7 \cdot 10^{-1}$ | $4.0 \cdot 10^{-5}$—$9.5 \cdot 10^{0}$ | $2.4 \cdot 10^{5}$ |
| bones and bone marrow | 380 | $1.5 \cdot 10^{-1}$ | $1.0 \cdot 10^{-5}$—$3.5 \cdot 10^{0}$ | $3.5 \cdot 10^{5}$ |

Section 1: Investigated organ or tissue
Section 2: Number ($n$) of examined specimens
Section 3: Median value ($m$) of concentrations of $^{232}$Th in mg per g tissue
Section 4: Smallest ($c_{min}$) and greatest ($c_{max}$) concentration of $^{232}$ Th in a sample in mg per g tissue
Section 5: Ratio of greatest to smallest concentration ($Q = c_{max}/c_{min}$)

Table 5. Group III: Organs and tissues with a median value $10^{-1} > m \geqq 10^{-2}$ mg $^{232}$ Th/g tissue

| Organ/Tissue | $n$ | $m$ (mg/g) | $c_{min}$—$c_{max}$ (mg/g) | $Q = \frac{c_{max}}{c_{min}}$ |
|---|---|---|---|---|
| cervical lymph nodes | 6 | $7.8 \cdot 10^{-2}$ | $5.0 \cdot 10^{-2}$—$1.5 \cdot 10^{0}$ | $3.0 \cdot 10^{1}$ |
| adrenal gland | 12 | $3.7 \cdot 10^{-2}$ | $2.0 \cdot 10^{-4}$—$4.8 \cdot 10^{-1}$ | $2.4 \cdot 10^{3}$ |
| galbladder and bile ducts | 9 | $2.4 \cdot 10^{-2}$ | $2.0 \cdot 10^{-5}$—$1.2 \cdot 10^{-1}$ | $6.0 \cdot 10^{3}$ |
| hypophysis | 6 | $1.6 \cdot 10^{-2}$ | $8.6 \cdot 10^{-4}$—$5.8 \cdot 10^{-2}$ | $6.7 \cdot 10^{1}$ |
| lung | 28 | $1.4 \cdot 10^{-2}$ | $1.0 \cdot 10^{-5}$—$2.5 \cdot 10^{-1}$ | $2.5 \cdot 10^{4}$ |
| intervertebral disc | 7 | $1.4 \cdot 10^{-2}$ | $1.0 \cdot 10^{-5}$—$4.7 \cdot 10^{-2}$ | $4.7 \cdot 10^{3}$ |
| pancreas | 10 | $1.2 \cdot 10^{-2}$ | $3.6 \cdot 10^{-3}$—$1.2 \cdot 10^{-1}$ | $3.3 \cdot 10^{1}$ |
| colon | 25 | $1.1 \cdot 10^{-2}$ | $1.0 \cdot 10^{-5}$—$3.2 \cdot 10^{-2}$ | $3.2 \cdot 10^{3}$ |
| small intestine | 21 | $1.1 \cdot 10^{-2}$ | $2.0 \cdot 10^{-5}$—$5.5 \cdot 10^{-2}$ | $2.8 \cdot 10^{3}$ |
| bronchus | 11 | $1.1 \cdot 10^{-2}$ | $1.9 \cdot 10^{-3}$—$1.5 \cdot 10^{-2}$ | $7.9 \cdot 10^{0}$ |

Section 1: Investigated organ or tissue
Section 2: Number ($n$) of examined specimens
Section 3: Median value ($m$) of concentrations of $^{232}$ Th in mg per g tissue
Section 4: Smallest ($c_{min}$) and greatest ($c_{max}$) concentration of $^{232}$ Th in a sample in mg per g tissue
Section 5: Ratio of greatest to smallest concentration ($Q = c_{max}/c_{min}$)

Table 6. Group IV: Organs and tissues with a median value $10^{-2} > m \geqq 10^{-5}$ mg 232 Th/g tissue

| Organ/Tissue | $n$ | $m$ (mg/g) | $c_{min}-c_{max}$ (mg/g) | $Q = \frac{c_{max}}{c_{min}}$ |
|---|---|---|---|---|
| trachea | 8 | $9.5 \cdot 10^{-3}$ | $3.0 \cdot 10^{-5} - 7.6 \cdot 10^{-2}$ | $2.5 \cdot 10^{3}$ |
| kidney | 22 | $9.5 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 3.2 \cdot 10^{-2}$ | $3.2 \cdot 10^{3}$ |
| testis | 6 | $8.9 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 5.3 \cdot 10^{-3}$ | $5.3 \cdot 10^{2}$ |
| vagina | 3 | $8.1 \cdot 10^{-3}$ | $7.7 \cdot 10^{-3} - 1.3 \cdot 10^{-2}$ | $1.7 \cdot 10^{0}$ |
| dura mater | 11 | $7.9 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 6.3 \cdot 10^{-2}$ | $6.3 \cdot 10^{3}$ |
| stomach | 8 | $7.6 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 1.6 \cdot 10^{-2}$ | $1.6 \cdot 10^{3}$ |
| esophagus | 8 | $7.5 \cdot 10^{-3}$ | $8.0 \cdot 10^{-5} - 4.0 \cdot 10^{-2}$ | $5.0 \cdot 10^{2}$ |
| pericardium | 5 | $7.0 \cdot 10^{-3}$ | $5.4 \cdot 10^{-3} - 1.2 \cdot 10^{-2}$ | $2.2 \cdot 10^{0}$ |
| a.pulmonalis | 14 | $6.4 \cdot 10^{-3}$ | $3.7 \cdot 10^{-4} - 8.8 \cdot 10^{-2}$ | $2.4 \cdot 10^{2}$ |
| a.hepatica | 4 | $5.8 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 1.2 \cdot 10^{-2}$ | $1.2 \cdot 10^{3}$ |
| a.iliaca | 24 | $5.5 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 1.4 \cdot 10^{-2}$ | $1.4 \cdot 10^{3}$ |
| aorta | 29 | $5.2 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 1.2 \cdot 10^{-2}$ | $1.2 \cdot 10^{3}$ |
| a.renalis | 6 | $4.7 \cdot 10^{-3}$ | $1.8 \cdot 10^{-4} - 2.4 \cdot 10^{-2}$ | $1.3 \cdot 10^{2}$ |
| prostate | 5 | $4.3 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 1.3 \cdot 10^{-2}$ | $1.3 \cdot 10^{3}$ |
| atrium | 16 | $4.3 \cdot 10^{-3}$ | $2.0 \cdot 10^{-5} - 8.4 \cdot 10^{-3}$ | $4.2 \cdot 10^{2}$ |
| ureter | 6 | $3.9 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 1.7 \cdot 10^{-2}$ | $1.7 \cdot 10^{3}$ |
| veins | 42 | $3.7 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 5.9 \cdot 10^{-2}$ | $5.9 \cdot 10^{3}$ |
| skin | 15 | $3.6 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 1.7 \cdot 10^{-2}$ | $1.7 \cdot 10^{3}$ |
| aa.cerebrales | 8 | $3.4 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 4.3 \cdot 10^{-3}$ | $4.3 \cdot 10^{2}$ |
| cardiac ventricle | 25 | $3.4 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 1.1 \cdot 10^{-2}$ | $1.1 \cdot 10^{3}$ |
| appendix | 4 | $3.3 \cdot 10^{-3}$ | $2.0 \cdot 10^{-5} - 1.2 \cdot 10^{-1}$ | $6.0 \cdot 10^{3}$ |
| connective tissue | 27 | $3.2 \cdot 10^{-3}$ | $8.0 \cdot 10^{-5} - 6.9 \cdot 10^{-2}$ | $8.6 \cdot 10^{2}$ |
| mamma | 5 | $3.2 \cdot 10^{-3}$ | $4.2 \cdot 10^{-4} - 1.3 \cdot 10^{-2}$ | $3.1 \cdot 10^{1}$ |
| a.subclavia | 12 | $3.1 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 1.7 \cdot 10^{-2}$ | $1.7 \cdot 10^{3}$ |
| urinary bladder | 6 | $2.9 \cdot 10^{-3}$ | $3.2 \cdot 10^{-4} - 1.5 \cdot 10^{-2}$ | $4.7 \cdot 10^{1}$ |
| coronary arteries | 22 | $2.7 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 6.4 \cdot 10^{-3}$ | $6.4 \cdot 10^{2}$ |
| cardiac valves | 12 | $2.7 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 8.7 \cdot 10^{-3}$ | $8.7 \cdot 10^{2}$ |
| tongue | 6 | $2.6 \cdot 10^{-3}$ | $2.0 \cdot 10^{-5} - 7.8 \cdot 10^{-3}$ | $3.9 \cdot 10^{2}$ |
| thyroid | 10 | $2.3 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 2.4 \cdot 10^{-2}$ | $2.4 \cdot 10^{3}$ |
| a.femoralis | 8 | $2.1 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 5.2 \cdot 10^{-2}$ | $5.2 \cdot 10^{3}$ |
| striated muscle | 35 | $2.1 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 3.4 \cdot 10^{-2}$ | $3.4 \cdot 10^{3}$ |
| meniscus | 4 | $1.9 \cdot 10^{-3}$ | $2.3 \cdot 10^{-4} - 3.4 \cdot 10^{-3}$ | $1.5 \cdot 10^{1}$ |
| a.carot. comm. | 8 | $0.9 \cdot 10^{-3}$ | $2.0 \cdot 10^{-5} - 4.1 \cdot 10^{-3}$ | $2.1 \cdot 10^{2}$ |
| capsule of the knee joint | 3 | $0.3 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 2.4 \cdot 10^{-3}$ | $2.4 \cdot 10^{2}$ |
| nervous system | 28 | $0.3 \cdot 10^{-3}$ | $1.0 \cdot 10^{-5} - 6.3 \cdot 10^{-3}$ | $6.3 \cdot 10^{2}$ |

Section 1: Investigated organ or tissue
Section 2: Number ($n$) of examined specimens
Section 3: Median value ($m$) of concentrations of $^{232}$Th in mg per g tissue
Section 4: Smallest ($c_{min}$) and greatest ($c_{max}$) concentration of $^{232}$Th in a sample in mg per g tissue
Section 5: Ratio of greatest to smallest concentration ($Q = c_{max}/c_{min}$)

Tables 3–6 show the results of the neutron activation analysis. The various sections contain the following data:

Section 1: Investigated organ or tissue.

Section 2: Number (n) of examined specimens.

Section 3: Median value (m) of concentrations of $^{232}$Th in mg per g tissue.

Section 4: Smallest ($c_{min}$) and greatest ($c_{max}$) concentration of $^{232}$Th in a sample in mg per g tissue.

Section 5: Ratio of greatest to smallest concentration

$$\left(Q = \frac{c_{max}}{c_{min}}\right).$$

The organs and tissues are grouped according to their average mean value.

Group I (Table 3) comprises organs and tissues containing $m > 10^0$ mg $^{232}Th$ per g tissue.

Group II (Table 4) comprises organs and tissues containing $10^0 > m \geqq 10^{-1}$ mg $^{232}Th$ per g tissue.

Group III (Table 5) comprises organs and tissues containing $10^{-1} > m \geqq 10^{-2}$ mg $^{232}Th$ per g tissue.

Group IV (Table 6) comprises organs and tissues containing $10^{-2} > m$ mg $^{232}Th$ per g tissue.

For this table, we chose the median value of concentration as well as the smallest and greatest range of concentration, since in many organs and tissues it is impossible to determine a meaningful mean concentration.

## D. Discussion

### *a) Deposition of $^{232}Th$ in the Body*

In earlier histologic and autoradiographic investigations (Wegener and Zahnert, 1970) we had believed that organs existed (the complete nervous system, for instance) where no $^{232}Th$ was deposited. The highly sensitive method of neutron activation analysis shows, however, that no organ or tissue of the human body remains free of $^{232}Th$ after intra-arterial injection of thorotrast. This ubiquitous deposition is understandable. The administration of thorotrast is comparable to vital staining, using trypan blue, pyrol blue, or lithium carmine. This technique was developed by Ribbert (1904) and Goldmann (1909, 1910, 1913), and, in recent years, has been related to thorotrast by Grampa and Ferrario (1967). Although these dye materials are mainly stored in the RES proper, they can be found throughout the entire system, that is to say they can be seen in the so-called RHS (= reticulohistiocytic system; new nomenclature), suggesting that they are also in the histiocytes of the connective tissue all over the body. When Aschoff (1924) outlined this system, he was very much influenced by the results of vital staining. This readily explains the deposition of $^{232}Th$ over the whole body. After intra-arterial injection of thorotrast, the $ThO_2$ particles reach the reticulohistiocytical system (RHS) very quickly via the bloodstream. The sugar component (dextrin), however, which stabilizes the injected solution, is separated in the blood immediately after intra-arterial injection.

### *b) Concentration of $^{232}Th$ in Various Organs and Tissues*

The organs of the reticuloendothelial system show the highest median concentration: spleen, liver, bone marrow, and lymph nodes. This fact was hitherto well established. The lymph nodes around the portal fissure and in the surrounding tissue of the pancreas show the highest median concentrations, followed by liver and spleen. This distribution suggests that certain quantities of $^{232}Th$ get carried

away from the liver and also from the spleen via the lymph tracts into the lymph nodes of the immediate surroundings. These three most important places of deposition of $^{232}$Th are followed by: lymph nodes in more remote areas of the body (para-aortae, parahilar), bone marrow, and tonsils. These organs also form part of the reticuloendothelial system proper. All other organs belong to the RHS; here the median concentrations of $^{232}$Th are about 2–3 decimal exponents lower than in the organs of the RES proper. The adrenal gland and the pituitary gland were placed by Aschoff (1924) in the RES. Their median concentration of $^{232}$Th seems to prove this to be correct. Certain important organs and tissues (i.e., ovary and uterus) are not mentioned in the tables. We measured only one or two concentration values.

### *c) Distribution of $^{232}$Th in Organs and Tissues*

Our results in Tables 3–6 prove that $^{232}$Th in all organs and tissues is distributed inhomogeneously. This is shown clearly in the wide range between maximum and minimum concentrations, but is even more evident in the quotients $\frac{c_{max}}{c_{min}} = Q$ which range from $2.2 \times 10^0$ in the pericardium to $2.4 \times 10^5$ in the lymph nodes at the bifurcation of the aorta, and to $3.5 \times 10^5$ in bone and bone marrow. There is no recognizably regular pattern for this quotient. There is also no dependence on the concentration since the lymph nodes of the liver-spleen axis show a very low Q level ($3.9 \times 10^1$), while those at the bifurcation of the aorta show a very high Q level ($2.4 \times 10^5$). These very diverging Q levels of the lymph nodes reveal most clearly that there is no dependence on the sum total of stored $^{232}$Th.

Hursh et al. (1957), Hursh (1967), and Parr (1967) had drawn attention to the inhomogeneous deposition before we did. In spite of this, the total amount of $^{232}$Th in an organ, the resulting radiation dose, and the possible development of tumor growth was again and again concluded from concentrations in specimens of organs and tissues. According to our results, this conclusion is only partly justifiable. In such evaluations or assessments, relatively minor mistakes may occur for the lymph nodes of the liver-spleen axis. Major errors may, however, occur in evaluations for the liver, where these data would be most important, because of the tumor frequency in this organ.

A statement about the percentage distribution of the total amount of thorotrast in the various compartments of the RES (RHS) is therefore only partly correct and this is also likely to be the case when we look at the percentage-distribution of thorotrast deposited in the various compartments in relation to the compartment liver. A number of factors are responsible for the development of such inhomogeneous deposits:

1. In a very small percentage of cases the variable amount of injected thorotrast could be seen to be responsible. Generally, the amount of injected solution lay between 20 and 80 ml. These variable amounts with a difference of factor 4 between minimum and maximum concentration, cannot totally explain the big Q values.

2. The total amount of thorotrast injected plays a part in that, with small amounts of it, more will remain in the spleen than if a bigger quantity had been used, in which case this part of the RES would be set with thorotrast (Hale and

Baillif, 1953). This effect, caused by great quantities of thorotrast, was, in earlier years, used when blocking the RES in order to generate a shock (Bennsinger et al., 1971). Only after very large amounts of thorotrast do bone marrow, lymph nodes, and lungs store it intensively during the initial period following injection (Kabisch, 1967). In addition, the ability of the macrophages to phagocytose changes. Kabisch (1957, 1967) showed in rat experiments that the number of cells storing was dependent on the amount of thorotrast injected.

3. The injection site is important: If injected in the neck region, the cervical, hilar, and paratracheal lymph nodes contain more $^{232}$Th than in cases where the contrast dye was injected into the inguinal region and vice versa. This phenomenon is probably coherent with the fact that, however exactly and carefully the injection has been carried out, small paravascular deposits develop which are carried away via the lymph tracts. In cases where these paravascular deposits can be detected macrocopically, the different concentration in the lymph nodes of various body areas is particularly marked. Hale and Baillif (1953) were able to prove this in animal experiments.

4. Previous diseases of an organ will influence the organ's ability to store. Fibrous lymph nodes resulting from tuberculosis, or from chronic nonspecific lymphadenitis, can store much less $^{232}$Th than intact ones. A liver after hepatitis, cholangitis, or fatty degeneration with portal or intralobular fibrosis will show a different storage capacity than an intact organ. Silva Horta et al. (1961) have observed that dilatation of the spaces of Disse—in the area or region of which the lymph tracts of the liver are thought to lie—cause difficulties in transporting away the lymph and consequently the thorotrast remains in one place for a longer period of time.

5. Immediately after storage of $^{232}$Th in an organ of the RES a "dispute" commences between the tissue, the foreign body, and the radioactivity. After a while, there will be fibrosis, cells disintegrate which are however replaced via regeneration from cells in the neighborhood. Later, however, this process leads to the formation of cicatricial tissue. Lymph and blood vessels obliterate, $^{232}$Th is phagocytosed by cells and, after their death, liberated again, thereby starting the cycle all over again (Anders and Leitner, 1932; Easton, 1952; Baillif, 1953). This constant changing around of the stored material leads to structural alteration of the organ. The liver can lose its intimate structure and become cirrhotic. In addition, from the first moment of storage, subsequent nuclides of disintegrated $^{232}$Th occur. These only accelerate the above-mentioned organ change because they are also radioactive and disintegrate into new and again, radioactive elements. Rüger (1969) has shown in extensive animal experiments that thorotrast is, at first and for some hours, stored in muscle, heart, thymus, and other organs, after which it is released into the organs of the RES. This storage and releasing effect does not take place in a uniform manner and so the individual distribution to the organs will be influenced.

6. It was not possible in all cases to free the organ parts completely from the attached connective and fatty tissue. This fact explains some very high Q levels in organs with low median concentration of $^{232}$Th (for instance in veins). Inevitably, $^{232}$Th is measured which is incorporated in adjacent tissue.

7. Bell (1953) has shown that the *collodial stability* was important for a homogeneous distribution of thorotrast if used as a contrast dye. This stability, however, is lost during hydrolysis of dextrin which takes place at different times in the various organs.

*d) Concentration and Late Effects*

Late effects, as shown in Table 2, occur only in concentration groups I and II. It is important to note that malignant tumors developed exclusively in the liver. Only in one case did we find a benign tumor and that was in the spleen. There is therefore no dependence of the tumor frequency on the median concentration of $^{232}$Th. This is also made clear in the late effects of the lymph nodes of the liver-spleen axis.

The animal experiments revealed very soon that the simple relationship $c\,t = constant$ (c = concentration of poison) (Druckrey and Kupfermüller, 1948, 1949) does not apply to tumor procreation by means of thorotrast (Wenz, 1964). On the contrary, there are numerous factors, quantitatively not yet conceivable, involved in the development of thorotrast tumors. They are:

1. Absolute quantity of $^{232}$Th in the organ
2. Number of irradiated cells
3. Self-absorption of the aggregated material that was deposited in the various organs in different degrees. In autoradiographic and histologic investigations, Wegener and Zahnert (1970) and Wegener et al. (1973) have made it obvious that, for instance, in the spleen, $^{232}$Th is, on the whole, deposited in larger clusters. As a result of this, the self-absorption rate is much higher than, for instance, in the liver, where $^{232}$Th is deposited in the form of the smallest aggregates or single particles of thorium dioxide.
4. Unspecific radiation effects in the organ and its surrounding tissue (i.e., fibrosis) with increased radiation absorption
5. Transport of thorium in the organ during lifetime
6. Stimulus caused by a foreign body (here: $^{232}$Th).

We conclude from our investigations that we can, with a high degree of probability, make the following statements:

1. Late effects after thorotrast injection occur only in the organs of the RES proper, that is to say, in the sites of deposition of the highest median concentration of $^{232}$Th.

2. Tumors occur frequently in the liver. This is the organ not with the highest median concentration, but with the maximum absolute quantity of $^{232}$Th and therefore with the greatest number of "altered" cells.

3. All organs in the concentration groups III and IV (except for lymph nodes in group III) show no late effects. This means that tumors which developed in these organs after injection of thorotrast are probably not caused by the radioactive contrast medium, no matter whether radiation, or the stimulus provided by a foreign body is blamed for tumor production, or both factors together. The latter fact also applies for various nontumor diseases with mutation in certain organs, such as Addison's disease (adrenal atrophy), diabetes mellitus, general arteriosclerosis, nephritis, so-called prostatic hypertrophy, goiters, and many others. One exception may possibly be the lung which is exposed addition-

ally to radiation via exhaled thoron. This knowledge is important in the formulation of the expert's opinion. For not all thorotrast patients will suffer the complication of a "tumor"; some dying of diseases unconnected with thorotrast during the latency period. Then, all too often, a causality between thorotrastosis and death is assumed.

In this context it would be pertinent to discuss the development of so-called double carcinomas in general human thorotrastosis. Wuketich and Mark (1957) and Budin and Gershon-Cohen (1956) have presented cases with not only malignant liver tumors, but also additional carcinomas in the direct neighborhood of thorotrast organs (splenieflexure of the colon). These authors related the carcinomas in the neighborhood of thorotrast organs to deep irradiation produced by the radioactive contrast medium and its by-products. It should be mentioned, however, that the alpha particles of $^{232}Th$, only have a maximum penetration range of 83 mμ. There is no beta irradiation with $^{232}Th$ and the gamma-ray production is quite poor in energy (0.059 MeV). The by-products of $^{232}Th$ develop in such a small quantity and are often nuclides with a high proportion of alpha rays. They also are rapidly diluted by the bloodstream and a high percentage of them are mobilized from spleen, liver, and lymph nodes. It is therefore true to say that the development of carcinomas in the neighborhood of thorotrast organs as a result of radiation is highly unlikely. It is much more probable that in cases of double carcinoma, a thorotrast patient has by chance developed a second carcinoma.

## References


Anders, H. E., Leitner, Z.: Über die röntgenologische Darstellung von Milz, Leber, Knochenmark durch Thoriumdioxyd und ihre histologischen Grundlagen. Klin. Wschr. **11**, 1097–1100 (1932)

Aschoff, L.: Das reticuloendotheliale System. Ergebn. inn. Med. Kinderheilk. **26**, 1–118 (1924)

Ballif, R. N.: Splenic reactions to colloidal thorium dioxide in the albino rat. Amer. J. Anat. **92**, 55–115 (1953)

Barousch, R.: Thorotrastschäden. Wien. med. Wschr. **119**, 681–685 (1969)

Bell, E.: The origin and nature of granules found in macrophages of the white mouse following intravenous injection of thorotrast. J. cell. comp. Physiol. **42**, 125–136 (1953)

Bensinger, M. A., Keller, M., Merrell, L. F., O'Leary, M. D.: Thorotrast-induced reticuloendothelial blockade in man. Clinical equivalent of the experimental model associated with patent pneumococcal septicemia. Amer. J. Med. **51**, 663–668 (1971)

Benstedt, J. P. M.: Experimental studies in mice on the late effects of radioactive and non-radioactive contrast media. Ann. N.Y. Acad. Sci **145**, 728–737 (1967)

Budin, E., Gershon-Cohen, J.: The danger of cancer from thorotrast as a diagnostic medium. Amer. J. Roentgenol. **75**, 1188–1193 (1956)

Druckrey, H., Küpfmüller, K.: Cit. in Wenz, 1964 (1948)

Druckrey, H., Küpfmüller, K.: Cit. in Wenz, 1964 (1949)

Edgington, D. N.: The estimation of thorium and uranium at the submicrogram level in bone by neutron activation. Int. J. appl. Radiat. **18**, 11–18 (1967)

Editorial: Vinyl chloride, P. V. C., and cancer. Lancet (**1974 I**), 1323

Editorial: Vinyl chloride and cancer. Brit. med. J. **1974 I**, 590–591

Easton, T. W.: The role of macrophage movements in the transport and elimination of intravenous thorium dioxide in mice. Amer. J. Anat. **90**, 1–33 (1952)

Fruhling, L., Gros, Ch.-M., Batzenschlager, A.: Sarcome endothélial angioplastique généralisé chez un malade ayant subi 12 ans auparavant une injection intra artérielle et para-artérielle de thorotrast. Bull. Ass. franç. Cancer. **42**, 559–563 (1955)

Futh, U., Pietske, H. U.: Hämangioendotheliome der Leber nach Thorotrastapplikation vor 30 Jahren. Fortschr. Röntgenstr. **121**, 398 (1975)
Goldmann, E. E.: Die äußere und innere Sekretion des gesunden und kranken Organismus im Lichte der vitalen Färbung. Bruns' Beitr. klin. Chir. **64**, 192–265 (1909)
Goldmann, E. E.: Die innere und äußere Sekretion des gesunden und kranken Organismus im Lichte der vitalen Färbung. Verh. dtsch. Ges. Path. 14. Tag. 138 (1910)
Goldmann, E. E.: Der Verdauungsvorgang im Lichte der vitalen Färbung. Verh. d. 30. Kongr. f. inn. Med. (1913)
Grampa, G., Ferrario, I.: Thorotrast e Trypanblau: Azione biologica generale ed effetti sul sistema reticoloistiocitario epatico. Studia Ghisleriana **1567**, 206–222 (1967)
Grampa, G., Tommasini Degna, A.: Hemangioendothelioma of the liver following intravenous injection of thorotrast. Acta genet. (Basel) 8, 65–78 (1958)
Hale, A. R., Ballif, R. N.: The retention and elimination of colloidal thorium dioxide in the albino rat following protracted administration. Anat. Rec. **117**, 163–174 (1953)
Hofbauer, K., Häring, R.: Intraabdominelle Blutungen bei angioplastischem Sarkom der Leber als Folge einer Isotopen-Spätschädigung (Thorotrast). Med. Welt **13**, 569–572 (1970)
Hohenstatt, H.: Multiple Hämangiosarkome in der Leber nach zerebraler Angiographie mit Thorotrast. Hippokrates (Stuttg.) **36**, 227–228 (1965)
Hursh, J. B.: Loss of thorium daughter by thoriumdioxide patients. Ann. N.Y. Acad. Sci. **145**, 634–641 (1967)
Hursh, J. B., Steadman, L. T., Looney, W. B., Colodzin, M.: The excretion of thorium and thorium daughters after thorotrast administration. Acta radiol. (Stockh.) **47**, 481–497 (1957)
Kabisch, W. T.: Quantitative studies of phagocytosis by means of thorotrast. Anat. Rec. **128**, 447–465 (1957)
Kabisch, W. M.: Phagocytosis of colloidal thorium dioxide and cobaltic oxide by the reticuloendothelial system of the rat. Ann. N.Y. Acad. Sci. **145**, 585–594 (1967)
Kaick, G. van, Scheer, K. E.: Actual status of the German thorotrast study. Risø Report **294**, 157–162 (1973)
Kampmann, H., Krauss, O., Rüger, W., Scheer, K. E., Lorenz, W. J.: Quantitative Organverteilungsuntersuchungen mit Thorotrast durch Neutronenaktivierungs-Analyse. Verh. dtsch. Ges. Nukl.-Med. **6**, (1968)
Kampmann, H., Wesch, H., Wegener, K.: Quantitative Thorium-Bestimmungen in 30 Organen bei menschlicher Thorotrastose. 7. Jahrestagg. d. Ges. Nuclearmed. 25–27. 9. 69 Zürich (1969)
Kaul, A., Heyder, J.: Zeitlich-räumliche Verteilung von Thorium-Folgeprodukten nach Incorporation von kolloidalem $ThO_2$ (Thorotrast). In: Radioisotope in Pharmakokinetik und klinischer Biochemie. Stuttgart-New York: Schattauer 1970
Kemnitz, P.: Multizentrische angioplastische Retikuloendotheliomatose der Leber nach Thorotrast-Arteriographie. Zbl. allg. Path. path. Anat. **106**, 189–197 (1964)
Lange, C. E., Jühe., S., Veltman, G.: Über das Auftreten von Angiosarkomen der Leber bei 2 Arbeitern der PVC-herstellenden Industrie. Dtsch. med. Wschr. **99**, 1598–1599 (1974)
Lee, F. I., Harry, D. S.: Angiosarcoma of the liver in a vinylchloride worker. Lancet (**1974I**), 1316
Lüdin, Jr., M.: Hämangio-Endotheliomatose von Leber und Milz bei Thorotrastspeicherung. Schweiz. Z. allg. Path. **16**, 987–994 (1953)
Parr, R. M.: Information on thorotrast dosimetry supplied by the radiochemical analysis of tissue specimens. Ann. N.Y. Acad. Sci. **145**, 644–653 (1967)
Ribbert, H.: Die Abscheidung intravenös injizierten gelösten Carmins in den Geweben. Z. allg. Physiol. **4**, 201 (1904)
Riedel, W., Müller, B., Kaul, A.: Non-radiation effects of thorotrast and other colloidal substances. Risø Report **294**, 281–293 (1973)
Roe, F. J. C.: Vinyl chloride and cancer. Brit. med. J. **1974II**, 176
Scheer, K. E., Krauss, O., Varga, L.: Neutronen-Aktivierungsanalyse zur Bestimmung von Thorotrast in Gewebsproben. Atompraxis **13**, 451–453 (1967)
Silva Horta, Da J., Collete, J., Luz Roriz, Da M.: Circulation lymphatique du foie. Visualisation du réseau lymphatique du foie chez des individus injectés avec le thorotraste. Arch. De Vecchi Anat. pat. **35**, 1–24 (1961)

Silva Horta, Da J., Abbatt, J. D., Cayolla Da Motta, L., Roriz, M. L.: Malignancy and other late effects following administration of thorotrast. Lancet **1965II**, 201–205

Wegener, K., Kampmann, H., Wesch, H.: Verteilung und Wirkung von Thorotrast im menschlichen Körper (Bericht über path.-anat. und quantitative Untersuchungen an 6 Obduktionsfällen). Herbsttag. d. dtsch. Pathologen, 10.–12. 10. 1969, Wiesbaden

Wegener, K., Kampmann, H., Wesch, H.: Lymphknotenveränderungen bei menschlichen Thorotrastosen (patholog.-anat., autoradiographische und quantitative Untersuchungen mittels der Neutronen-Aktivierungsanalyse). Jahrestag. d. Vereinig. Südwestdtsch. Röntgenologen u. Nuklearmediziner, Freiburg, 21.–23. 9. 1972

Wegener, K., Wesch, H., Kampmann, H.: The reticuloendothelial system (RES) in human thorotrastosis (pathological, radioautographic and quantitative studies of nine autopsies.) 6th Intern. Meeting of the reticulo-endothelial society, Freiburg 28. 7.–1. 8. 1970

Wegener, K., Wesch, H., Kampmann, H.: Reticuloendotheliales System und Thorotrastose nach diagnostischer Angiographie. Dtsch. med. Wschr. **51**, 1977–1981 (1971)

Wegener, K., Wesch, H., Kampmann, H., Zahnert, R.: Pathological findings in the RES (liver, spleen, lymph nodes, bone marrow) of thorotrast patients. Risø Report **294**, 248–258 (1973)

Wegener, K., Zahnert, R.: Bericht über pathologisch-anatomische und autoradiographische Untersuchungen an 9 Fällen menschlicher Thorotrastose. Virchows Arch. Abt. A **351**, 316–332 (1970)

Wenz, W.: Thorotrasttumoren. Quantitative Untersuchungen über das Dosis-Wirkungsproblem bei der Thorotrastose. Ergebn. Chir. Orthop. **46**, 81–166 (1964)

Wesch, H., Kampmann, H., Wegener, K.: Assessment of organ distribution of thorium by neutron-activation analysis. Risø Report **294**, 52–60 (1973)

Wuketich, S., Mark, Th.: Doppelcarcinom nach Thorotrast-Arteriographie. Z. Krebsforsch. **62**, 95–108 (1957)

Prof. Dr. K. Wegener
Pathologisches Institut der
Städt. Krankenanstalten
Bremserstr. 79
D-6700 Ludwigshafen
Federal Republic of Germany