The History of Chloracne and Dioxin

A Skin Disease
at the Crossroads
of
Occupational, Environmental and Political Concerns

A Paradigm
of
Endocrine Disruption

by

Gérard TILLES[a]
Olivier SORG[b] & Jean-Hilaire SAURAT[c]

[a] Bibliothèque Henri-Feulard, Hôpital Saint-Louis, Paris
[b] Université de Genève, Centre Médical Universitaire, Swiss Center for Applied Toxicology
[c] Professeur émérite de dermatologie, Université de Genève.

Introduction

Dermatologic manifestations
Seminal observations
Additional cases
Complementary studies of pathological alterations. Pathophysiological approach
Current features
Puzzling dermatoses : chloracne or not chloracne?

Chloracne-associated events
Chloracne : cutaneous stigmata of industrial activities
Industrial electrolysis in question
Chloronaphthalene and chlorobiphenyls as causal agents
The “Perna Krankheit”
The 1930s to 1950s outbreak
First steps of an industrial “epidemic”
Chloracne, “sentinel event” of systemic toxicity
Additional cases of chloronaphthalene toxicity. Outbreak in the US Navy
Occupational exposure to polychlorinated biphenyls
Epilogue

From Nitro to Seveso
Monsanto plant, Nitro, West Virginia
First cases
Epidemiologic studies
Controversies surrounding Monsanto’s reports and their reliability
Nordrhein-Westfalen
Badische Anilin und Soda Fabrik AG [BASF], Ludwigshafen
Boehringer, Hamburg : evidence of 2,3,7,8 tetrachlorodibenzo-*p*-dioxin responsibility
Philips-Duphar, Amsterdam
Diamond Alkali, New Jersey
Dow Chemical, Michigan
Experiments on prisoners
Additional chloracne cases
Rhône-Poulenc, Pont-de-Claix, France
Spolana plant, Czechoslovakia
Coalite and Chemical Products Ltd, Bolsover
Seveso, Italy
Initial observations

Further epidemiology studies
Investigations on long term adverse health effects

Additional cases among trichlorophenol exposed workers

Miscellaneous chemicals associated with occupational chloracne

Chloracne-associated food poisoning

Yusho [Japan, 1968],Yucheng [Taiwan, 1979] paradigms of chloracne associate food poisoning

Additional episodes of food contamination

Chloracne : elusive effect of Agent Orange in the Vietnam war

From domestic to tactical uses of herbicides
Operation “Ranch Hand”, military aftermath of herbicides use
First concerns and controversies
Reassuring statements, additional concerns
Veterans’ claims
Further investigations. The “Ranch Hand” Program
Additional veterans claims. Further debates and controversies. Political interferences
Focusing on chloracne and skin diseases
Evaluation of the health effects of Agent Orange : a “conflict between science and social concerns”
The “almost forgotten” Vietnamese population

Chloracne, dioxins and politics : the Yushchenko case

Political background
Timeline of a medical and detective story
Evidences and denials of dioxin intentional poisoning
Victor Yushchenko as a medical case
How and why did VY go to Geneva
Which were the organs affected ?
Which specific treatments were used ?
How was dioxin clearance sped up ?

Chloracne, hazardous wastes and municipal solid waste incinerators

Love Canal
The Times Beach and Missouri episodes
The Valley of Drums
Municipal solid waste incinerators. Controversies in France
General situation
Medical investigations in the population of Maincy

Concluding remarks

Appendices

Appendix I : Chloracne seminal observations

S. von Bettmann, Heidelberg, 1897
K. Herxheimer, Frankfurt am Main, 1899
G. Thibierge, Paris, 1899
G. Thibierge, Ph. Pagniez, Paris, 1900
L. Rénon, C. L. M. Latron, Paris, 1900
H. Hallopeau, P. Lemierre, Paris, 1900
H. Hallopeau, M. Trastour, Paris, 1900
P. Fumouze, Paris, 1901
A. Jaquet, Basel, 1902
W. Wechselmann, Berlin, 1903
W. Lehmann, Freiburg, 1905
J. Nicolas, M. Pillon, Lyon, 1926
J. Nicolas, J. Lacassagne, Lyon, 1929

Appendix II : Chloracne events

Appendix III : Summary of findings in occupational, environmental and veterans studies regarding the association between specific health problems and exposure to herbicides

Appendix IV : Dioxins and dioxin-like chemicals

Appendix V : Carcinogenicity and adverse developmental effects of dioxins : a controversial matter

Cited references

Abbreviations

AMA	*American Medical Association*
AhR	*aryl hydrocarbon receptor*
CYP	*cytochrome P450*
2,4-D	*2,4-dichlorophenoxyacetic acid*
DCA	*3,4-dichloroaniline*
DDT	*1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane*
EPA	*Environmental Protection Agency (US)*
IARC	*International Agency for Research on Cancer*
IOM	*Institute of Medicine*
I-TEQ	*international toxic equivalency*
MADISH	*Metabolizing acquired dioxin-induced skin hamartoma*
MSWI	*Municipal solid waste incinerators*
NAS	*National Academy of Sciences*
NIOSH	*National Institute for Occupational Safety and Health*
PAB	*p-aminobiphenyl*
PCB	*polychlorinated biphenyl*
PCDF	*polychlorinated dibenzofuran*
PCN	*polychlorinated naphthalene*
PCP	*pentachlorophenol*
POP	*persistent organic pollutant*
SMR	*standardized mortality ratio*
STS	*soft-tissue sarcoma*
2,4,5-T	*2,4,5-trichlorophenoxyacetic acid*
TCAB	*3,3',4,4'-tetrachloroazobenzene*
TCAOB	*3,3',4,4'-tetrachloroazoxybenzene*
TCB	*1,2,4,5-tetrachlorobenzene*
TCP	*2,4,5-trichlorophenol*
TCDD	*2,3,7,8-tetrachlorodibenzo-p-dioxin*
TEF	*toxicity equivalency factor*
TEQ	*toxic equivalent*
VA	*Veterans Administration/Affairs*
VAVA	*Vietnam Association of Victims of Agent Orange*
VY	*Victor Yushchenko*

Introduction to chloracne history

It seems logical to consider that dermatology is the oldest medical discipline, since the skin is the only organ directly visible. Indeed, records exist for the description of skin diseases by the Ancient Egyptians dating back to 2000 BC. However, modern dermatology, involving a systematic description and classification of skin diseases, with an attempt to deduce a treatment, only started to develop during the second half of the 18th century.

The skin is the largest organ of the body and, with an external surface of 1.7-2m^2, any morphological change (following / due to?) various environmental or systemic stresses will be fully visible. The skin is in direct contact with the environment, and hence will be the first target organ following exposure to pathogenic microorganisms, xenobiotic chemicals or physical stressors. Pathophysiological changes of the skin may also be the consequence of diseases of the internal organs. The possibility of observing the skin directly renders dermatology a (distinctive?) medical discipline, and dermatologists have developed a rich teminology to describe the various skin (manifestations / diseases and disorders?).

It has been known for a long time that the appearance of the skin may be affected by various conditions. These changes can manifest themselves as a rash, erythema, discoloration, (atrophic changes / atrophy?) or inflammation. A skin rash (is observed following / can follow?) exposure to heavy metals, such as lead, mercury or thallium, as well as during viral, bacterial or fungal infections, such as zona, syphilis or mallasezia. Other metals, such as nickel, chromium and cobalt, may induce contact dermatitides, whereas arsenic may induce hyperpigmentation, hyperkeratosis and squamous cell carcinoma. Sunburn, solar urticaria and actinodermatitis are common following acute exposure to the sun, whereas photoageing is the consequence of long-term exposure to the sun. All these conditions have been observed since the beginning of the Christian era, although their description has evolved over time, becoming progressively more precise with the development of dermatology over the last 200 years.

Acne vulgaris is a very common skin condition that has probably affected most adolescents for millennia. It seems, however, that it has been considered as a true disease only since the 6th century, when Aetius Amidenus, a physician in Constantinople, named “ionthos” (ίονθωξ,) or “acnae” the lesions occurring on the face at the “acme” (ἀκμή) of life, which at that time might have referred to puberty.

At the turn of the 20th century, strange cases of acne began to appear in workers engaged in the production of caustic soda or potash by the electrolysis of sodium or potassium chloride, with the release of chlorine gas. In the first decades of the 20th century, such acneiform eruptions appeared in workers on the sites of production of chlorinated pesticides, in particular polychlorinated naphthalenes. When considering the conditions leading to these strong acne-like eruptions not related to puberty, it appeared that the common denominator was the presence of chlorine gas,

chlorination reagents and/or chlorinated organic compounds. In 1899, Karl Herxheimer, Professor of Skin and Venereal Diseases at the new University of Frankfurt (Germany), was the first to establish relationships between chlorine in a large sense and the development of these strange acneiform eruptions, and so introduced the term “chloracne” for this new skin condition.

Since the middle of the 20th century, several industrial accidents involving the production or the use of 2,4,5-trichlorophenol [TCP] (why square brackets?), as well the use of TCP-related herbicides by the US army during the Vietnam War, , pointed to the by-product 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [TCDD] as the causative agent for the development of chloracne. More recently, the team led by Professor Jean-Hilaire Saurat at Geneva University Hospital, during the medical care of the former Ukrainian president Victor Yushchenko, who had been poisoned by TCDD during his presidential campaign, (made a better characterisation / provided a better description?) of chloracne lesions, which are not true acne lesions, and not necessarily induced by chlorine or chlorinated compounds.

This review is dedicated to the history of chloracne and similar cutaneous syndromes, from 1897, with the first cases of industrial workers exposed to chlorine and its derivatives, to 2004, with the poisoning of Victor Yushchenko by TCDD, and including major industrial accidents during the period as well as the use of phenoxy herbicides during the Vietnam War.

Dermatologic manifestations

Seminal observations

The history of chloracne originates from a fortuitous observation. On March 1, 1897, Siegfried Bettmann [1869-1939], Privat Docent in Heidelberg University’s Department of Medicine, was presented with two patients whose “faces were speckled with a infinite number of thin black points located in the pilosebaceous ostia. There were also large comedones on the forehead, external ears and behind them, intermixed with small nodules and pustules […] Large comedones were also visible on the beard area and the scalp […] on the chest, back, lateral aspects of the neck and on the nape of the neck […] The skin of the face looked dark-grey, rough and dry. […] Sebaceous cysts were visible on the penis […] The patients, previously strong men, claimed of unusual tiredness and loss of appetite […] Both patients said that their symptoms occurred since they had been in charge of the cleansing of towers filled with hydrochloric acid.” [(Bettmann, 1901) *transl. G. Tilles*] Due to the fact that the walls of the towers containing the hydrochloric acid were protected by tar, Bettmann suspected tar was responsible for the disease.

Regarding the pathological features, Bettmann focused on “corps ronds” [sic] and “grains” [sic] he saw in the follicle walls, which were similar to those observed in Darier's disease although not as

numerous. He inferred that a process of keratinization might be involved. Following these observations, Bettmann had the opportunity to examine 21 additional workers engaged in identical occupations who had developed similar symptoms, all more severe as the patients had been exposed for a longer time to the same chemical.

Although Bettmann was probably the first to observe patients exposed to chlorine and suffering from a cutaneous eruption looking like acne vulgaris, Karl Herxheimer [1861-1942] (Figure 1), Head of the Department of Dermatology at Frankfurt am Main City Hospital, was the first to establish a causal relationship between chlorinated compounds and the cutaneous lesions.

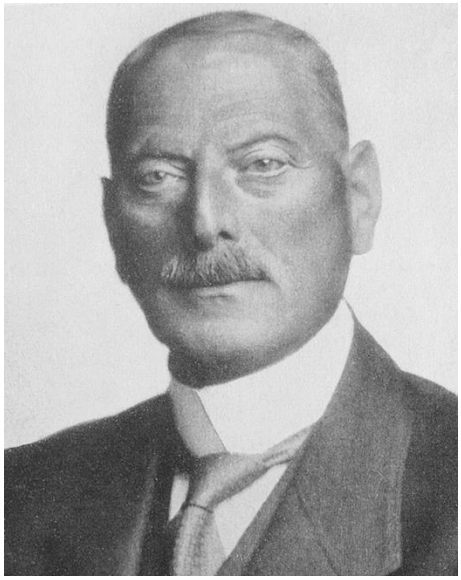


Figure 1. Karl Herxheimer (1861-1942). Coll. G. Plewig.

On February 28, 1899, Herxheimer published the description of a male patient aged 22 whose appearance he qualified "ungewöhnlich" (i.e. "uncommon" (Herxheimer, 1899)). The face, neck, back, chest and proximal parts of the limbs were covered with nodules, tubercles, pustules and an "infinite number of comedones". Some tubercles and nodules were excoriated or ulcerated. Moreover, wrote Herxheimer, since the beginning of the cutaneous disease "the patient had been coughing and spitting[…] He is very thin and does not sleep anymore." The patient mentioned that the cutaneous signs had appeared from the first days he had been working in a factory producing caustic potash through electrolysis of potassium chloride

However, "two months after the patient left the factory, new tubercles and abscesses still appeared. The general condition of the patient remained altered." *[transl. G. Tilles]* Three other employees working in the same plant exhibited the same cutaneous signs.

Pointing out the fact that the afflicted skin was sometimes covered with clothes, he inferred that this strange acne was not related to a direct action of chlorine on the skin but more likely to chlorine gas, first inhaled then excreted by the sebaceous glands. He also indicated that his colleague Wolff Griesheim had seen several patients working in a similar occupational environment who complained about the same skin alterations. With regard to aetiology, Herxheimer stated that "chlorine was undoubtedly the cause of the eruption". A few years later, in 1901, lecturing at the Congress of the German Society of Dermatology in Breslau, he changed his mind and proposed that the causal agents were chlorinated hydrocarbons and not the chlorine itself (Herxheimer, 1901; Holzmann, 1907). He also suggested regarding the disease as a "suppurated and indurated acne vulgaris" with an unusual extension and location that reminded him of acnes caused by iodides or bromides. Finally, Herxheimer coined the name "chloracne" to describe this unusual disease.

Better known by dermatologists for the description of the phenomenon occurring in syphilitic patients treated by mercury that commemorates his name, Karl Herxheimer was murdered on December 6, 1942 in the concentration camp in Theresienstadt (Herxheimer and Krause, 1902; Hundeiker, 2008).

These seminal cases, published within a few years of each other, mainly in Germany and in France, enriched the clinical features of this unusual “acne”.

Additional cases

In Paris, 14 cases of similar skin lesions were published under various names: “chloracné”, “acné chlorique”, “dermatose chlorique électrolytique” or later “gale du chlore” (Gougerot, 1952).

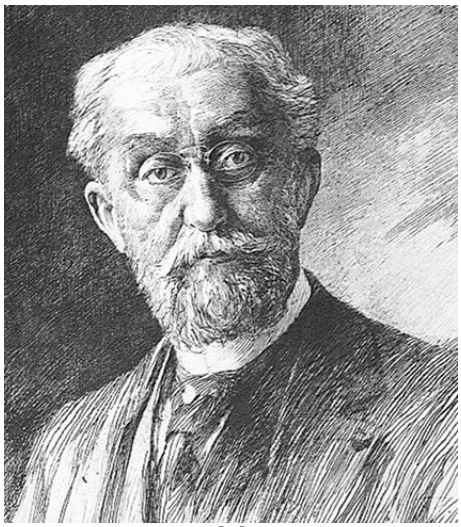


Figure 2. Georges Thibierge (1856-1926).

Coll. Henri-Feulard Library, Hôpital Saint-Louis, Paris.

The first one was published by Georges Thibierge [1856-1926] (Figure 2), head of La Pitié Hospital in Paris, under the name “acné comédon” (Thibierge, 1899). He described the clinical appearance of the patient and underlined the diagnostic value of the comedone, a “consistent lesion of chloracne”, although in the early stage of the disease, he failed to see any “difference between comedones observed in acne vulgaris and those in chloracne. Then morphological changes and secondary lesions modify the general aspect. The most frequent change is the dark coloration of the head of the comedones that become black.

Due to the abundance of comedones in some areas of the body the colour is striking. […] The colour is the consequence of the dryness of the superficial layers of comedones due to the alteration of the sebaceous glands; their secretion no longer spreads on the skin surface. Due to the great number of comedones and to the accumulation of a greasy substance in the sebaceous glands, the tegument can become thickened and infiltrated to a slight degree. In summary, the main clinical features of chloracne are the consequence of an oversecretion of sebaceous glands that leads to sebaceous cysts. The transformation into inflammatory lesions as seen in acne vulgaris are absent in chloracne. The lesions are formed in a few weeks. They vary according to the areas afflicted: on the face the lesions are predominant on the cheeks, nose and forehead. They are almost exclusively constituted by comedones that fill all the glands of the face, giving it the appearance that would be produced by a gunshot from a short distance. On the scalp, almost never afflicted with acne vulgaris, comedones can gather and form a greasy layer. The earlobes are massively afflicted; large comedones and sebaceous cysts can develop, some quite close to each other giving the earlobe the

appearance of a sebaceous sponge from which a sebaceous substance issues on the application of pressure(?). On the neck, comedones are numerous. On the trunk and limbs the lesions are usually less developed than on the face. Voluminous cysts may be seen on the upper back. On the genitalia, comedones may be extremely numerous, speckling the penis with grey or blacks dots. Cysts are visible on the ventral aspect of the penis and on the scrotum." *[transl. G. Tilles]*

Regarding pathological alterations, Thibierge was the first to underline those of the sebaceous glands: "the epidermis is not altered […] In the dermis, only the sebaceous glands are involved […] Few of them remain however intact. On almost every histopathological preparation, cystic cavities are more or less visible. Their walls are made by several rows of flattened cells. They contain more or less concentric and keratotic debris. […] An infiltrate of embryonic cells is visible around the cysts." *[transl. G. Tilles]* He also observed thin bacilli in the centre of the comedones, similar to those previously described by Paul Gerson Unna [1850-1929], the role of which Thibierge regarded as hypothetical (Thibierge and Pagniez, 1900a). Due to the unusual appearance of the patient, the psorospermosis described by Jean Darier [1856-1938] a few years before was regarded as a differential diagnosis (Darier, 1889). Attending Thibierge's presentation, Darier agreed and added that this disease is "obviously not an acne vulgaris".

On April 6, 1900, at the "Société Médicale des Hôpitaux de Paris", Louis Rénon and Charles-Louis-Marie Latron presented the case of a patient who exhibited an "acné comédon" on the malar crescents, earlobes and beard area similar to those previously described. The patient had been working for nine months in the same factory as Thibierge's and Hallopeau's patients in the production of chlorine and chlorinated lime (a bleaching mixture containing calcium hydroxide, chloride and hypochlorite) by sodium chloride electrolysis. Rénon and Latron hypothesized that the vapours of chlorine were responsible for the cutaneous disease and for the pulmonary tuberculosis the patient was afflicted with (Renon and Latron, 1900).

Continuing the series of chloracne patients, Henri Hallopeau title?) [1842-1919] (Figure 3), Thibierge's colleague at the Hôpital Saint-Louis, published two cases of male patients working in a plant producing chlorine who presented with the symptoms of this unusual occupational acne (Hallopeau and Trastour, 1900) (Figure 4).

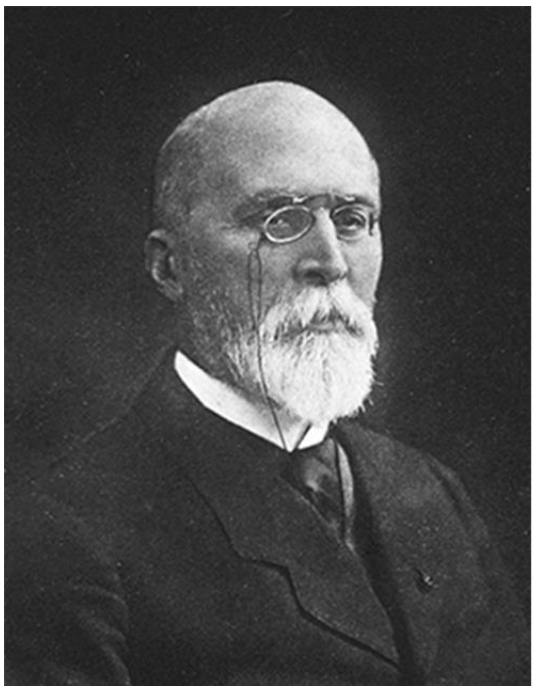


Figure 3. Henri Hallopeau (1842-1919). Coll. Henri-Feulard Library, Hôpital Saint-Louis, Paris.

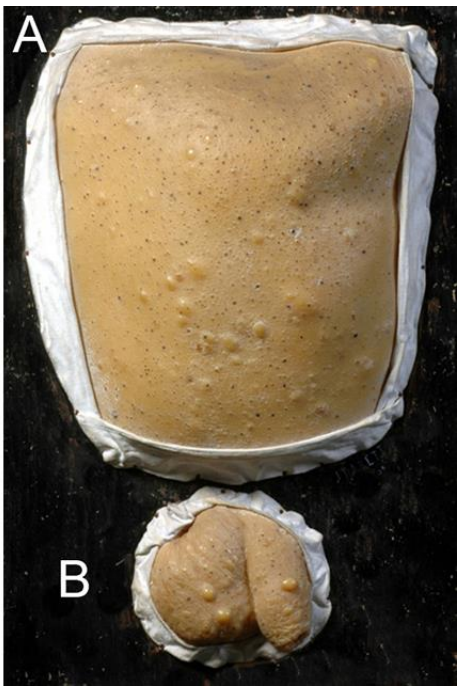


Figure 4. *Moulage n°2139. Coll. générale "Acné chlorique"*. Man aged 45, chlore worker (Obs. Hallopeau, 1900). A. Right aspect of the back. B. Penis and scrotum, right side. Two mouldings, Musée de l'Hôpital Saint-Louis, Paris.

Hallopeau underlined the differences between the lesions observed on covered and uncovered areas: only the latter were afflicted with an intense black coloration whereas the legs and the back? exhibited inflammation of the sebaceous glands without dark pigmentation. In this regard, Hallopeau hypothesized the involvement of two substances: one, probably chlorine, might be responsible for the inflammation of the pilosebaceous follicles, for the comedones and for the general symptoms (cough, bronchitis, tears); the other one, might be responsible for the darkening of the comedones on the uncovered areas of skin. In an additional presentation at the French Society of Dermatology, Hallopeau hypothesized that chlorine might be responsible for the hypersecretion of the sebaceous glands and for the solidification of sebum. The black colour of the comedones, however, was regarded as being the result of dust "imprisoned into the new layer of sebum" (Hallopeau, 1900). Attending Hallopeau's presentation, Raymond Jacques Adrien Sabouraud [1864-1938] contested this view pointing out that in every acne, "the black coloration of comedones is an ordinary fact in the pathogenesis of which there is no point in hypothesizing about the role of chlorine" (Hallopeau and Lemierre, 1900).

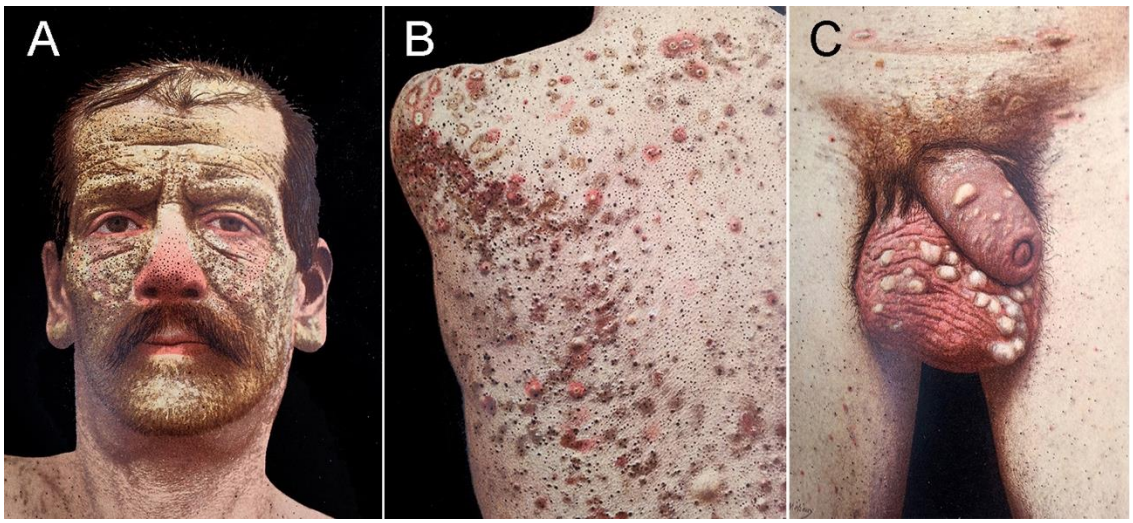


Figure 5. Patient with chloracne. (P. Fumouze): "Dermatose chlorique électrolytique". Imp. Chaix (Ateliers Chéret), Paris, 1901. A. Face. B. Back. C. Genitalia.

Paul Fumouze, Hallopeau's pupil, author of a thesis on chloracne, was, to the best of our knowledge, the first to publish clinical photographs of chloracne (Figure 5). He mentioned the oedema of the face as the first cutaneous sign. This vanished in a few days, sometimes followed by a fine desquamation that preceded the onset of the more typical cutaneous lesions. As he considered that nodules, papules and pigmented spots could not be regarded as symptoms of acne vulgaris, he preferred to name the disease "dermatose chlorique électrolytique" and gave the following vivid description: "a patient entered the hospital eight to ten months after he had begun to work in a factory where chlorine was produced by the electrolysis of sodium chloride. […] When called by his name, he comes closer quite slowly because walking is very painful. He is questioned; he can hardly hear; he is almost deaf. Coughing and spitting constantly, he talks with difficulty." Fumouze was also struck by the characteristic appearance of the "chloric face as it resembles a leprous face […] The face is thunderstruck and black; the skin is thick and rough when touched; hairs are rare; the scalp is bare, blackened, hardened […] and thick, like the skin of an elephant. The earlobes are filled with adipose masses, comedones and nodules. Under the eyes are two strips harder than the surrounding skin that make the eyelids, which are red due to chronic conjunctivitis, more visible. Comedones and nodules are disseminated over the whole face. A pachydermia, which looks as though it is tinted with black carbon and a thick, blackened scalp, scattered with a few hairs are usual in all men working in contact with sodium chloride electrolysis. When examining patients, one is struck by the generalization of the dermatosis […] no area is spared. Some of them are more afflicted than others: the chest and especially the back where comedones swarm. […] On the genitalia, there are numerous sebaceous cysts on the penis and the scrotum. […] some of the cysts are so large that they may handicap walking. Moreover, the patient sleeps night and day. Here is a man who has been working eight months in a plant producing chlorine by sodium chloride electrolysis; he has lost his vigour, he is now deformed, afflicted with a disease that nothing can cure or even improve. […] These workers fade gradually, they are shaken by coughing, their eyes

are afflicted with conjunctivitis, their sight darkens, the body, covered with cysts and comedones, becomes increasingly thin, they do not worry about their disease, they are quiet, resigned. […] A man after working a year or two at most in the factory is rubbish, useless for society" (Fumouze, 1901). *[transl. G. Tilles]*

Like his colleagues, Sabouraud underlined the unusual appearance of the patient: "the face is tattooed with powder grains; […] the sebaceous cysts are developed to such an extent that […] The skin seems filled with peas. […] The appearance of the subject becomes deformed and horribly ugly. If one adds the fact that the pilosebaceous ostia filled with comedones always lose the hair they contained, one will realize condition of the head of a man ravaged by chloracne." *[transl. G. Tilles]*. In conclusion, he pointed out that no basic symptom except its intensity could distinguish [chloracne] from an ordinary acne vulgaris (Sabouraud, 1902).

In Halle Ernst Fraenkel observed a male worker employed in a factory producing chlorine by electrolysis. He had a great number of comedones on the face, inflamed papules at the ostium of the sebaceous glands and carbuncles and sebaceous cysts the size of a cherry or of a walnut located on the trunk and on the penis (S., 1902).

In Basel Alfred Jaquet observed eight patients, all of them working in a chemical factory in Rheinefelden [Great Dukedom of Bade] where chlorine was also produced by sodium chloride electrolysis (Jaquet, 1902). The number of chloracne cases incited the health services to investigate the occurrence of chloracne among the workers. The investigation was held on November 10, 1904 and 130 workers were examined. Of these, 39 were afflicted either with a few comedones the localisation of which was in favour of chloracne or with a more severe form of the disease consisting of a greyish colour of the face and numerous comedones, sebaceous cysts and abscesses. The wives and children of the workers were also included by the investigation. Among the wives, eight had a few comedones. Among the 27 children examined: 5, aged from 2 to 17, exhibited small comedones in the areas usually afflicted by chloracne. No sebaceous cysts were noticed. Regarding the disease of the children, Eduard [1862-1915] Jacobi hypothesized two possibilities: either they were exposed to the chlorinated derivative when bringing meals to the workers in the plant or they were exposed to impregnated working clothes at home.

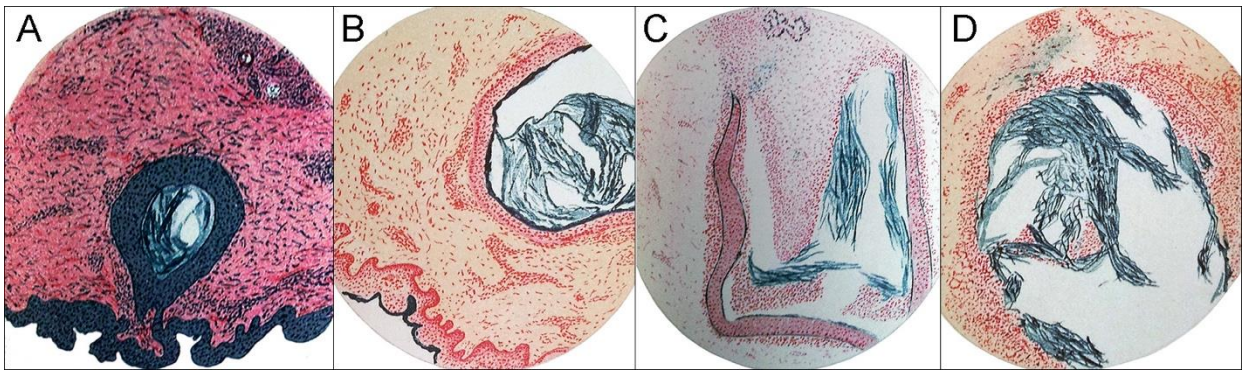


Figure 6. Histopathology of chloracne. W. Bornemann : "*Über die Histologie der Chloracne*". Arch f Dermatol Syphilol, 1902, 62: 75-90. A. Little corneous cysts connected to the surface of epidermis; an infiltrate surrounding sudoral glands is visible up and right on the image. B. Larger corneous cyst; the epithelium of the wall remains intact; a slight infiltrate is visible around the blood vessels. C. Schematic representation of the penetration of the infiltrate inside the corneous cysts. D. Schematic representation of a thick infiltrate around a corneous cyst; the infiltrate is in some places already between the corneous parts; only a small part of the content of the corneous cyst is (drought?)***.

Wilhelm von Bornemann [Frankfurt am Main] authored the first article devoted to the histopathology of chloracne (Figure 6). He observed the main alterations in the deeper part of the dermis: sebaceous cysts, corneous cysts smaller and more superficial than the sebaceous cysts and a third type of cyst that contained corneous material and an infiltrate of leucocytes. Bornemann hypothesized that the sebaceous cysts were the consequence of the sebaceous retention of sebum either in the sebaceous glands or in the sebaceous ducts, the epithelium of which proliferated or in some cases disappeared. He also suggested that chlorine might alter the quantity or quality of sebum. He noted the presence of an abundant pigment in the deep epidermal layers, forming yellowish-brown grains. As he saw the pigment was close to the leukocytes that infiltrated the epidermis, he concluded that the pigmentation was not native but was transmitted from dermis to epidermis by leukocytes. As for the sebaceous cysts, Bornemann showed images of the corneous content of some cysts, their destruction by the cellular infiltrate and the final replacement of the cysts by corneous particles (Bornemann, 1902).

On April 24, 1903, at the medical meeting in Freiburg in Breisgau, Lehmann presented the case of a male patient aged 38, working in a factory producing chlorine by the same process afflicted with the same cutaneous disease : comedones on the face and penis, sebaceous cysts on the chest and genitalia. Moreover, the patient's wife noticed the occurrence of comedones on her face - mainly around the eyes and on the temples - forearms, near the elbows, and legs, since she had been living in a house next to the factory. One of the patient's children, aged 18 months, also presented (with?) a great number of comedones on the forehead and cheeks that gave him a grey-brown appearance. A smaller number of black points were also visible on the earlobes, on the nose, on the lips, around the chin, and on the penis. Lehmann published 26 complementary observations of patients working in an identical occupational environment (Ärtzte, 1903).

Jacobi, Head of the Freiburg Hospital's Department of Dermatology, had the opportunity to examine the manager of an industrial chemical company whose face was covered with small

comedones, mainly on the wrinkles of the forehead. Comedones were also visible on the axilla, the chest, the back, the nape of the neck and the penis. A few sebaceous cysts were present behind the earlobes. According to the patient, several men working in the same plant exhibited similar lesions after they had been exposed to a chemical process using *p*-nitrochlorobenzene. The cutaneous lesions vanished after the exposure ceased. Lehmann [Freiburg] had the opportunity to observe two of these patients several years after they had found a new occupation. Cutaneous lesions still occurred. The first one had been employed on a farm for two years. He was healthy, although carbuncles sometimes still appeared. Numerous scars were visible on the nape of the neck, the back and on the retroauricular areas. Comedones remained on the face, notably on the forehead, the nasolabial folds, the thighs and the penis. The second patient had been employed as a doorman for four years. A few scars were also visible. No lesion was observed on the back and buttocks. Carbuncles occurred sometimes on the umbilicus. The penis was free from lesions but a few grains the size of millet were still present on the scrotum. The lesions remained mainly on the face and arms where numerous comedones were still visible (Lehmann, 1905a).

Finally, a few years after Herxheimer's seminal publication, about 80 cases had been published.

Concerning the evolution of the disease, the clinicians observed that in most cases the lesions slowly vanished after the exposure ceased. According to Hallopeau and Lemierre "one month after the patient was admitted to the Hôpital Saint-Louis, the lesions of the limbs have disappeared. […] On the face, the lesions remain; however, an improvement is visible" (Hallopeau and Lemierre, 1900). Thibierge and Pagniez confirmed Hallopeau's conclusions: "the lesions entirely healed. […] Then, the workers can go back to their work without fear." *[transl. G. Tilles]*

After the reports of Herxheimer and his French colleagues had been published in 1899 and 1900, Bettmann realized that his patients were afflicted with chloracne and authored four pages on the matter. He also noted that the forehead, behind the earlobes, the trunk, neck and back and most notably, the penis and scrotum were the areas most afflicted with comedones. He described small hard-looking, corneous, brownish nodules between the comedones. Whitish nodules occurred after long exposure to chloride derivatives. In a few cases, several hundred of them were disseminated over the whole body, though mainly located behind the earlobes and on the neck, scrotum and penis. The dorsum aspect of the hand and fingers speckled by little squamous papules, looked like a pityriasis rubra pilaris or Darier's disease. He also noted a diffuse, dirty, brown-grey pigmentation of the face, dry and rough to such a extent that the resemblance to the face in Darier's disease was striking, "frappante Ähnlichkeit" he wrote (Bettmann, 1901).

Regarding the designation of the disease, R. P. White [London] - author of a treatise on occupational dermatosis for which he coined the word "dermatergoses" - proposed a semantic evolution. Chloracne, wrote White, is "misnamed" as it is usually studied "separately from coal, oil and pitch dermatosis to which it undoubtedly belongs, in deference to common usage" (White, 1929). Although the pertinence of naming the disease "chloracne" was questioned and still is

(Saurat and Sorg, 2010), the majority of authors continued to use the word Herxheimer gave birth to (Herxheimer, 1912).

Complementary studies on pathological alterations. Pathophysiological approach

Like Bornemann and Thibierge, who stressed on the disappearance of the sebaceous glands, O. Gans also described the alteration of the sebaceous cysts that evolved into corneous masses and the infiltrate made of round cells that invaded the walls of the cysts and finally destroyed them (Gans, 1925). Regarding the inflammatory reaction, H. Grimmer considered it was caused by sebaceous glands filled with corneous material that behaved as foreign bodies (Grimmer, 1955).

W. Braun, author of the only monograph so far on chloracne, summarized the pathological features in three points: the epidermal alterations [acanthosis, hyperkeratosis] play a secondary role; the cystic alterations of the dermis originate in the follicles; either an increase of sebaceous gland activity or a pathological cornification or both can be responsible for the cystic alterations (Braun, 1955a). Finally, concluded Braun, the essence of chloracne "consists in an abnormal cornification. The sebaceous glands are never dilated but on the contrary are destroyed" (Figure 7) (Braun, 1955b).

Following these observations from the 1950s, several authors proposed a dynamic approach, studying pathological alterations of chloracne experimentally induced with various chlorinated derivatives on humans and animals.

G. W. Hambrick and Blank showed that applications of Halowax 1014 – a mixture of penta- and hexachloronaphthalene - to the ear canal of albinos rabbits for five consecutive days caused, within 48 hours, hyperkeratosis, thickening of the epidermis and a striking decrease in the size and number of the sebaceous gland acini. If prolonged applications were carried out, the epidermal changes progressed further and follicular plugging masses [comedones] appeared. The epidermis andsebaceous glands returned to normal over the six weeks after the applications of Halowax ceased (Hambrick and Blank, 1956).

Figure 7. Cornified (keratinized) sebaceous cyst. W. Braun : "Chlorakne. Akneartige Hautveränderungen durch chlorierte aromatische Kohlenwasserstoffe. Aus der Universitäts-Hautklinik Heidelberg". Coll. Walther Schönfeld, 1955.

At the Chicago meeting of the Society for Investigative Dermatology, on June 9, 1956, Hambrick presented complementary outcomes of his experiments. After applications of chloronaphthalenes to the back of six Caucasian and four adult male volunteers without acne vulgaris, there were at first (on the first and third days of Halowax application) no detectable changes. Then, "at 5 days […] the epidermal cells of the outer root-sheath forming the wall of the proximal portion of the infundibulum and the sebaceous gland duct epithelium of the large vellus follicles appeared to be increased in number. […] In addition an early decrease in the number of lipid-laden cells with the sebaceous gland acini of involved follicles was occurring. Within a few acini peripherally an increased number of squamous type cells were present. These latter cells were continuous with the epithelium of the sebaceous gland duct and contained no lipids. […] By the end of two weeks […] the involved follicles showed early dilatation of the infundibulum proximally. […] The sebaceous gland duct walls thickened and merged with the infundibular wall. Hyperplasia of the epidermal cells with incomplete keratinization was manifest by a thick parakeratotic cell layer surrounding a mass of keratinized epidermal cell(s?) which was beginning to fill the infundibulum proximally. Although no necrosis nor lysis of sebaceous gland cells was present and normal appearing acini were still present, definite diminution of sebaceous glands, both in number of cells and size of the acini was evident in the involved follicles. During the third to fifth week, […] sebaceous glands were practically absent. […] From the sixth to the twelfth week, large comedones were present in all follicular sites. […] Histologically, practically all follicles were reacting to the chlorinated naphthalene. […] Sebaceous gland acini were absent although occasionally a few fully developed cells remained attached at the periphery of the dilated follicle." Rothman, attending Hambrick's presentation, regarded these findings as "very intriguing".

As for the pathogenesis of this phenomenon, chemical necrosis or lysis of sebaceous gland cells seemed to Hambrich unlikely. Another possibility was that moderate concentrations of the highly chlorinated naphthalenes served as a constant stimulant of the epithelium of the external root sheath and sebaceous gland ducts. In this hypothesis, differentiation of the epithelium into squamous cells without further differentiation into sebaceous cells would occur. Therefore, Hambrick proposed, once the sebaceous cells already formed had served their holocrine role, no replacement for them becomes available. A third possibility, which Hambrick regarded as less tenable, was that the disappearance of sebaceous cells resulted from pressure atrophy secondary to comedone formation (Hambrick, 1957).

In France, P. Dugois and L. H. Colomb performed biopsies on eight patients affected by chloracne after the explosion at the Rhone-Poulenc plant [see later]. They described three phases of alterations, including the disappearance of sebaceous glands.The first one was marked by hyperacanthosis at the follicular ostium surrounded by a circular inflammatory reaction; the external layer of the pilosebaceous follicles thickened and the follicular ostium tended to be occluded. The second phase was characterized by the "keratinous cyst. The hair is isolated like a wick in the centre of an enormous oval cocoon surrounded by the epithelial wall of the cyst". The hair atrophied and

disappeared and this was followed by the complete disappearance of the sebaceous glands. The last phase was characterized by “the absence of inflammatory reaction; however, the sebaceous gland may behave as a foreign body in case of rupture provoked by pruritus.” No (vestige / trace?) of sebaceous glands was found (Dugois and Colomb, 1957).

A. M. Kligman and Shelley experimented with the application, for 35 days, of a mixture of penta- and hexachloronaphthalenes in mineral oil on various parts of the body of 31 male adults, aged 25 to 35, without any sign of acne vulgaris. Biopsies were performed 60 days after the application. The subjects experienced acne on each area where penta- and hexachloronaphthalene were applied. On the back, the results even exceeded the author’s expectation: “every man developed an alarming fulminant inflammatory acne indistinguishable from acne conglobata. To our mutual distress, the lesions were not confined to the sites of application but were extensive, appearing in distant areas to which they were transferred by hands or clothing.” Moreover the “acne” continued after the naphthalene applications had been discontinued, reached a climax in the fourth month and vanished slowly over the next six months leaving scarring of acne conglobata. On histopathological examination, the authors observed two major pathological events that confirmed the seminal observations: the entire follicular appendage had been transformed into a sack of keratin; the sebaceous glands had disappeared. They speculated that Halowax®, known as an irritant and a toxin, piles up in the follicles after the keratin plug has formed. The epithelial follicular wall was disrupted by the primary toxic effect of the chemical leading the follicular content to escape into the dermis where a violent inflammation was provoked by the primary toxic effect. Regarding the involution of sebaceous glands, they hypothesized it might be secondary to follicular occlusion and not to a direct chemical effect (Shelley and Kligman, 1957). The authors compared the comedone chloracne to a “time bomb”, a comparison Kligman also used when describing the pathogenic sequence from comedone to inflammatory lesions in acne vulgaris ["time bomb" which "explosion sets off the inflammatory process"] (Strauss and Kligman, 1960).

Interestingly, Strauss and Kligman proposed a pathogenic approach to the comedone formation in acne vulgaris close to the results they observed in experimentally induced chloracne. Examining the pathologic changes to sebaceous glands on more than 50 biopsy specimens from acne patients, they suggested that as the comedone forms, a variable degree of undifferentiation develops. Observing that the changes are similar to those that take place after plucking hairs, they concluded that the gland is influenced by any follicular disturbance, (especially horny distension of the follicle?). In this respect, the failure of sebaceous maturation and replacement by undifferentiated epithelial cells are considered as a response to various stresses, both chemical and physical or those related to comedones formation. Strauss and Kligman viewed this response as a (stereotyped?) defence of the gland that temporary ceases to synthesize specialized cellular products. Then, after the appearance of undifferentiated cells the sebaceous gland would have the potentiality to undergo keratinous metaplasia with the production of keratinized squames rather than sebaceous cells. In

fact, a gradual atrophy of the gland appears secondary to the comedone formation. Redifferentiation into specialized cells occurs when the inhibiting forces are removed (Strauss and Kligman, 1958).

Plewig induced chloracne in eight male adults, aged 21 to 30, by applying Halowax 1014, penta- and hexachloronaphthalene. Biopsies were then performed after one or two weeks, when comedones were not yet visible, after two to four weeks, when comedones were visible, and after 12 weeks. Cellular dynamics were studied with ^{3}H-thymidine, ^{3}H-glycine and ^{3}H-histidine. The initial pathological results confirmed those previously observed: squamous proliferation in the sebaceous glands and acanthosis in the upper part of the external root sheath. One or two weeks after the application of Halowax had ceased, corneocytes appeared in the sebaceous ducts. Then the sebaceous ducts became filled with a solid material made of keratinous basophilic cells. No sebaceous gland could be identified (Plewig, 1970). Plewig and Kligman underlined that the first pathological event is the disappearance of sebaceous glands with the transition of sebocytes into keratinizing cells. Then the pilosebaceous follicle produces masses of coherent corneocytes that distend the follicular duct and give rise to sterile comedones (Plewig and Kligman, 2000).

Suskind applied trichlorophenol derivatives daily for six weeks, both on his own forearms and on rabbit ears. On biopsies performed at intervals during the exposure and several weeks after the final exposure, he could observe that "the first indication of change is hyperkeratinisation in the sebaceous gland duct […] followed by plugging of the follicular orifice which occurs simultaneously with the alteration of the differentiation process of the acinar cells." He speculated that "the effect of the toxic agent is to cause the undifferentiated cells to become keratinocytes which produce keratin. […] What is most interesting is that, in some cases […] following the cessation of exposure, the complete pilosebaceous structure, including the sebaceous gland, is restored" (Suskind, 1985).

Cunliffe et al. performed electromicroscopic examination of samples of pilosebaceous keratin from workers exposed to a chlorinated hydrocarbon for a period of 12 months and from a control group with acne vulgaris. They found fewer *P. acnes* from patients with occupational acne than from those with acne vulgaris. They also found a significant increase in the percentage of squalene, wax esters and cholesterol and a decrease in free fatty acids and total triglycerides in patients with chloracne. The authors inferred from these findings that the industrial causal agent might act on the metabolism of the pilosebaceous unit, which could explain the clinical appearance of chloracne marked by numerous comedones [Kligman had previously showed the comedogenicity of high concentrations of squalene] (Cunliffe *et al.*, 1975; Kligman *et al.*, 1970).

In 1981, Moses and collaborators performed histopathological examination of the skin of 77 employees who had been working in a plant where 2,4,5-trichlorophenol [TCP] and 2,4,5-trichlorophenoxyacetic acid [2,4,5-T] had been produced from 1948 to 1969. The onset of chloracne had, therefore, occurred 13 to 32 years before the biopsies were performed. The workers were classed into three categories: those with clinically residual chloracne [48%]; those with a past history of chloracne but without current evidence of it [24%]; and those who had never had

chloracne [28%]. Solar elastosis was present in all subjects. Follicular infundibular dilatation, comedones and cysts were more frequent in subjects with current residual chloracne. The authors failed to find a significant difference between any of the chloracne groups in number, size or appearance of the sebaceous glands. Abnormal follicular changes, comedones and cysts were found in subjects with residual chloracne and among those who had never had chloracne. From these findings, the authors speculated that if corneous cysts were persistent markers of chloracne, they would have been found to the same degree in the people with current chloracne or with only a history of the disease. Finally, Moses et al. concluded that the histopathological changes of acute chloracne can be reversible which may indicate that in situations where prior exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin [TCDD] is uncertain, the presence or absence of pathological changes cannot be regarded as reliable indicators (Moses and Prioleau, 1985).

In 2002, Pastor et al. reported the case of a 45-year-old Ecuadorian man who had worked in different plants exposed to various fumes. Physical examination revealed the cutaneous signs of chloracne. In contrast with the authors who emphasized the disappearance of the sebaceous glands, Pastor et al. observed well-developed sebaceous glands and failed to see any squamous metaplasia of the sebaceous glands or ducts. They described follicular infundibula filled with keratotic plugs, mostly composed of orthokeratotic basket-weave basophiles, corneocytes and mature and well-developed sebaceous gland lobules at the base of many of the dilated infundibula (Pastor *et al.*, 2002).

Lee et al. published what they thought to be an unusual histopathological feature, which had, in fact, already been described by Bettmann. The patient was a 56-year-old Korean man exposed to herbicides during the Vietnam war. He had been affected for over ten years with numerous comedones filled with keratotic plugs on the scalp, retroauricular areas, chest and back, giving the appearance of typical chloracne. The histology of biopsy specimens indicated dilated hair follicles with a keratotic plug, acantholytic cells in the lower part of the follicular wall and a large number of “corps ronds” (Lee *et al.*, 2004). The authors quoted the observation previously published by Hayakawa et al., who reported comedonal papules on the scalp with acantholytic dyskeratosis (Hayakawa and Nagashima, 1995) and the case published by Nakagawa et al. of comedo-like acantholytic dyskeratosis of the face and scalp (Nagakawa *et al.*, 2000).

Current features

In 1985, Tindall estimated that about 4,000 persons were affected by chloracne. About half of them were probably poisoned by food. Since the 1990s, chloracne has become a rare disease - eight cases were reported in the UK between 1993 and 2011 - although its incidence might be underestimated due to the diseases included in the differential diagnosis (see further “Chloracne or Not Chloracne”) ([Anonymous], 2013).

Besides the erythematous rash that may occur on uncovered parts of the body a few hours after chloracnegen exposure, from the seminal observations all dermatologists have underlined the essential diagnosis value of the comedone. The “primary lesion of chloracne”, the comedone is regarded as the hallmark of chloracne and may even be the only lesion present. The comedones can even be so numerous they can affect every follicle “giving the appearance of (a) greyish sheet”, the patients looking as if they had Darier’s disease (Braun, 1970). Crow stressed the importance of the distribution of the lesions. He regarded of “considerable diagnostic importance” those “below and on the outer side of the eye [the so-called malar crescent] and behind the ear. […] They are the areas most likely to show residual lesions years after the more extensive chloracne has faded. Next in frequency come the cheeks, forehead and neck. […] The genitalia, both penis and scrotum, but particularly the latter, are sensitive regions” (Crow, 1981). Usually spared, “the nose is highly resistant and may appear as an island in a sea of lesions” (Tindall, 1985).

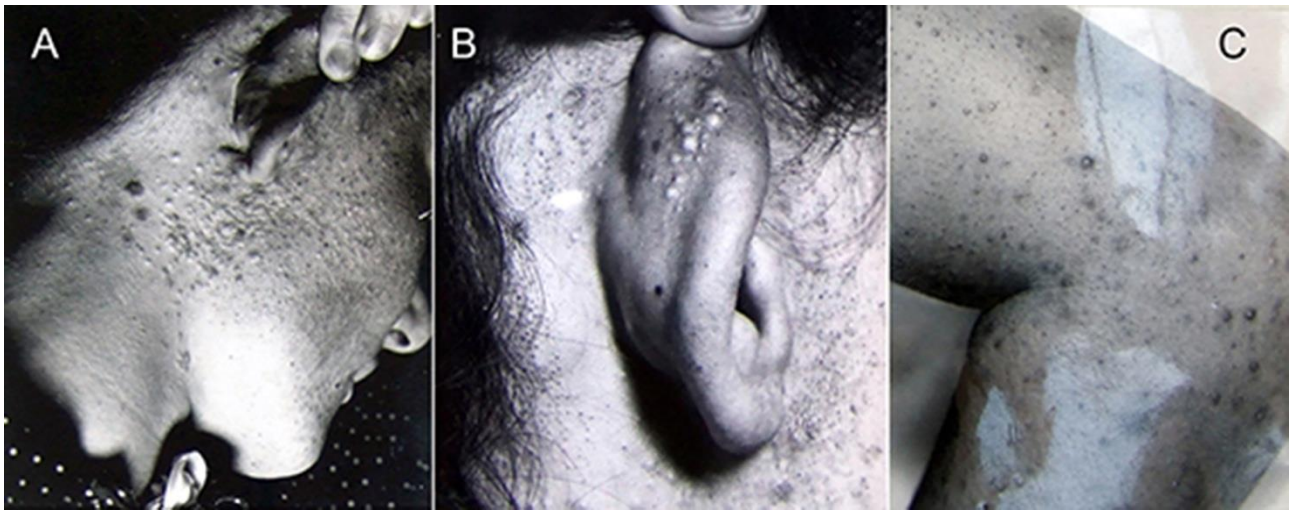
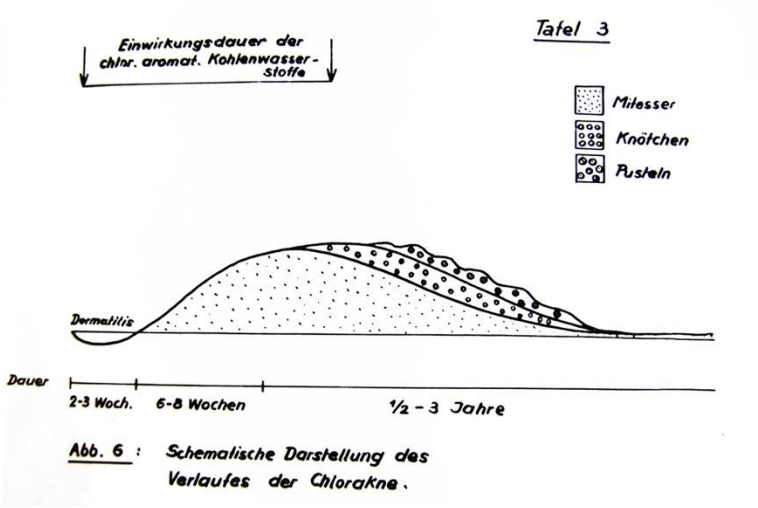


Figure 8. Comedones and sebaceous cysts in chloracne. W. Braun : “Chlorakne. Akneartige Hautveränderungen durch chlorierte aromatische Kohlenwasserstoffe”. Universitäts-Hautklinik Heidelberg. Coll. Walther Schönfeld, 1955. A. Face. B. Retroauricular area. C. Thigh and leg.

Other clinicians highlighted the diagnosis value of the cysts: “the most distinctive and almost invariable cutaneous lesions […] are the chloracne skin-coloured cysts, varying from 1 mm to as much as 1 cm in diameter. […] If these cysts are absent, then chloracne should be diagnosed with great caution, except in early or very mild cases” (Crow, 1970). Inflammatory lesions appear in the most severe cases, chloracne looking like a cystic acne. In the worst cases, chloracne may even look like acne conglobata, exhibiting inflammatory nodules and sinuses by fusion of epithelial channels. Scars may persist for up to 30 years, usually located on the malar regions and behind the ears (Zugermann, 1990) (Figure 8).



Braun (1955) proposed a schematic representation of the duration of the lesions: the erythema preceding comedones lasts two to three weeks, the cysts and pustules appear when the comedones are maximum i.e. six to eight weeks after the beginning of the disease that lasts two to three years (Figure 9).

Figure 9. Evolution of the chloracne lesions. W. Braun : "Chlorakne. Akneartige Hautveränderungen durch chlorierte aromatische Kohlenwasserstoffe". Universitäts-Hautklinik Heidelberg. Coll. Walther Schönfeld, 1955.

Besides the typical lesions, other skin symptoms have been described that completed the clinical appearance: hyperpigmentation mainly located on the face as illustrated by Japanese and Taiwanese patients [see later]; hypertrichosis on the temples that could be secondary to porphyria cutanea tarda sometimes associated with chloracne; follicular hyperkeratosis; conjunctivitis and alterations of the Meibomian glands - sometimes called ophthalmic chloracne - converted into squamous cysts that mainly affected the Japanese patients. Granuloma annulare-like lesions were observed in children after the Seveso accident. Palmoplantar keratoderma and sclerodactyly of fingers and toes also affected by chloracne were observed after many years of exposure to various chlorinated herbicides, two of them containing chloracnegens (Poskitt *et al.*, 1994).

Recent publications have stressed the absence of clinical specificity of the disease and have, therefore, emphasized the value of the pathological alterations related to structure loss: disappearance of the sebaceous glands "a key, almost diagnostic, feature" and structure additions: the "presence of epidermal cysts, either with an open comedone-like aspect or deeper in the dermis." After performing 52 biopsies on Yushchenko [see the Yushchenko case], Saurat et al. pointed out that all specimens showed identical aspects: disappearance of the sebaceous glands – none were apparant on 252 histological slides – and the appearance of cystic lesions the walls of which showed epidermal-like differentiation. These lesions, which the authors considered compatible with hamartomas, looking like comedones or infundibular cysts, had several characteristics: focal expression of the major dioxin-metabolizing CYP enzyme [CYP1A1] in the epithelial walls; mantle-like columnar epithelial downgrowths that might give birth to new cysts with the appearance of branching-cysts. The hamartomas created a new compartment that concentrated TCDD up to 10-fold compared to the serum (Saurat *et al.*, 2012). Due to the consistency of these pathological features, Saurat et al. questioned the reference to acne vulgaris and proposed the acronym MADISH [Metabolizing Acquired Dioxin-Induced Skin Hamartoma] that emphasized the value of the corneous cysts as a diagnostic tool (Saurat *et al.*, 2012). Passarini et

al. also insisted on the consistent absence of sebaceous glands, sometimes replaced by squamous metaplasia, and on the corneous hyperpigmentation (Passarini *et al.*, 2010).

Panteleyev et al. proposed that the transformation of the pilosebaceous unit induced by chloracnegens results from the accelerated exit of stem cells associated with a shift from the sebaceous differentiation to an epidermal one. Then, diminution of the sebaceous gland and the lower portion of the hair follicle with epidermal hyperplasia and hyperkeratinisation occur consequently. The switch of its content from semi-liquid sebum to solid keratin could explain infundibulum dilatation and comedone development (Panteleyev and Bickers, 2006).

Studying the effects of TCDD on skin samples *in vitro* and *ex vivo*, Ju et al. also hypothesized that TCDD affects differentiation of human sebocytes by switching the sebaceous into a keratinocyte-like differentiation. In this pathogenic hypothesis, the alteration ofsebocyte differentiation is regarded as the major reason for decreased lipogenesis and enhanced comedogenesis in chloracne (Ju *et al.*, 2011).

Polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans exert their biologic activities by binding to the intracellular aryl hydrocarbon receptor [AhR], a ligand-dependent transcription factor found in human keratinocytes and human sebaceous glands. The receptor-ligand complex migrates to the nucleus where it is bound to DNA sequences and modulates the transcription of target genes (Yamamoto and Tokura, 2003). Quite recently, Eyraud et al. published a study of two patients affected by metastatic melanoma and treated with BRAF-V600E inhibitors. Both patients exhibited facial cutaneous lesions looking like MADISH. Biopsies confirmed the absence of sebaceous glands. The authors hypothesized that additional molecular mechanisms could be involved (Eyraud *et al.*, 2015).

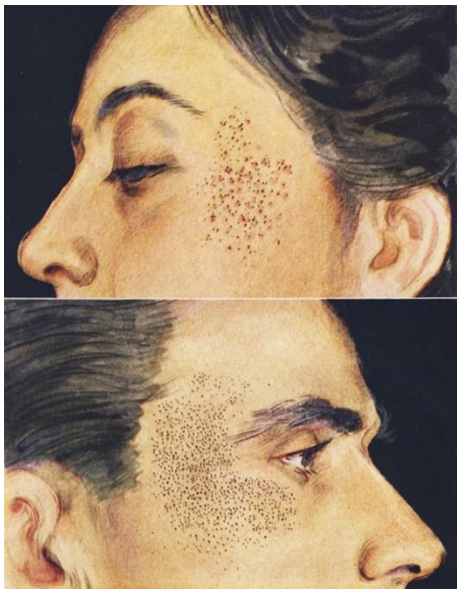
With regard to treatment, modalities used in acne vulgaris are ineffective in chloracne. Plewig and Kligman considered topical comedolytics, such as retinoids, as partially effective. Benzoyl peroxide is of no use. Topical and systemic antibiotics are useless. Oral isotretinoin may be useful in eliminating the comedones. High doses administered early in the course of the disease may prevent the onset of cysts (Plewig and Kligman, 2000). The absence of sebaceous glands in chloracne can explain isotretinoin inefficiency (Scerri *et al.*, 1995). Good aesthetic results have been obtained with light cautery under EMLA for comedonal chloracne (Yip *et al.*, 1993). In the Yushchenko case, incisions of the cystic lesions resulted in dystrophic healing. Mechanical dermabrasion and multiple micropunch extractions/aspirations healed quickly and were cosmetically satisfactory. The use of tumour necrosis factor α [TNF-α] inhibitors was used as a compassionate treatment (Saurat *et al.*, 2012).

Puzzling dermatoses : chloracne or not chloracne?

Besides the typical chloracne cases, several authors published case reports and articles about dermatoses looking like incomplete or mild forms of chloracne.

On December 17, 1931, Favre [Lyon, France] presented three male patients whose periorbital and temporal skin looked "speckled with blue-black dots and macules [...] mimicking the appearance given by some professional tattoos or by gun shots from a short distance. […] The black points were actually sorts of various sized comedones.[…] All patients were about fifty […] one of them had a few lesions on the earlobes." *[transl. G Tilles]* On pathological examination, Fabre observed cysts in the upper part of the dermis, limited (by / to?) two or three rows of epithelial cells. The content of the cysts was made of "squamous products of the epidermis." Fabre also pointed out the almost complete disappearance of the sudoral glands (Favre, 1932). Twenty years later, Favre and his pupil, Racouchot, authored an additional study of the disease now named after them (Racouchot, 1937). They also described the comedones intermixed with little yellow-pink nodules. They confirmed the pathological alterations and added the usual atrophy of the sebaceous glands. They also stressed the pathological aspect of the upper dermis which had the appearance described by Wagner as colloid milium (Favre and Racouchot, 1951). Due to the numerous open comedones and cysts that give it its striking appearance, the resemblance of chloracne to the dermatosis described by Favre and Racouchot has been pointed out (Cinque, 1986).

In 1944 and 1945, Doucas observed 15 patients, 14 woman and 1 man, afflicted with an eruption he regarded as unusual, made of "numerous comedones localized in temporozygomatic areas (Figure 10)." He noted that such an eruption had not been reported previously, either in North American or in foreign literature. Doucas hypothesized that the dietary deficiencies and the substitutes – both wheat and fat substitutes - prevalent during the war were contributing factors to the disease in predisposed patients. Apart from these factors, Doucas suggested that endocrino-sympathetic disturbances, nervous shock and the severe cold that occurred in December 1944 could produce hyperkeratosis. The use ofcosmetics containing the substitute oil obtained during the war – as reported in women using brilliantine - might also play a role. Histologic examination showed the replacement of sebaceous glands by keratinized cysts associated with atrophy of the hair follicles, flattening of the papillae and thinning of the prickle cell layer many of which were full of pigment (Doucas, 1947).



From February till the spring of 1946, in Basel, Schuppli observed an outbreak of a strange cutaneous disease. One hundred and fifty patients exhibited skin lesions that constituted three different clinical forms of the disease. The majority of the cases - 90%, mainly in children - had the appearance of an acne with comedones intermixed with tiny

Figure 10. Comedones localised in temporozygomatic areas. C. C. Doucas. Arch Derm Syphilol, 1947, 56 (3) : 376-378.

horny cysts occurring without preliminary inflammatory lesions. Comedones and microcysts, primarily located on the cheeks, nose and chin extended to the whole face in two or three weeks. Comedones were also observed on the forearms, nape of the neck, back and chest. In this first type, the pathological alterations were mainly marked by a follicular hyperkeratosis. In the most severe cases, the whole of the affected follicle was enlarged. Cysts were filled with corneous material. The sebaceous glands were present. No lesion was observed in the epidermis on the dorsal aspects of the hands. The second type of the disease, which looked like granuloma annulare, was seen in two families. Histologically, a thickening of the epidermis was noted. The third form was made of little papules similar to those of lichen ruber mixed with eruptive corneous cysts. The cutaneous lesions remained isolated during the whole course of the disease. Due to the onset of the lesions and the the fact that numerous cases appeared in such a short period, Schuppli coined the term keratosis follicularis “epidemica” to describe the disease, which he considered almost similar to the keratosis follicularis contagiosa described by Brooke [1893] and the keratosis follicularis described by Rocamora [1922]. He hypothesized a toxic origin although the precise cause remained unclear (Schuppli, 1947). Degos regarded Doucas and Schuppli’s observations as true chloracne cases (Degos, 1980). These clinical features may raise the question of the responsibility of hidden sources of chlorine in the daily environment for some cases and also lead to consideration of whether chloracne may be more frequent than the cases already published would seem to indicate.

Chloracne-associated events

Chloracne : cutaneous stigmata of industrial activities

Industrial electrolysis in question

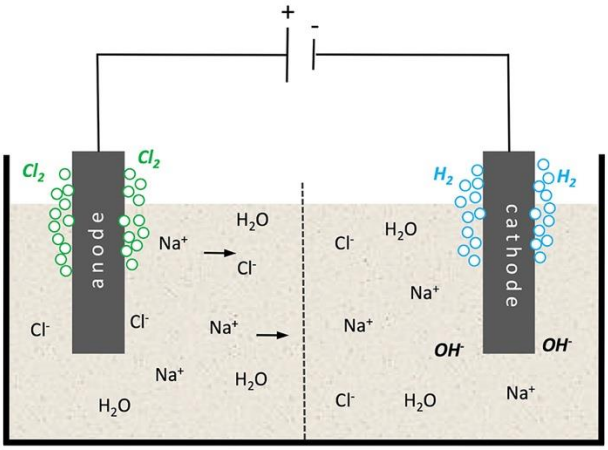


Figure 11. Simplified diagram of caustic soda production. A sodium chloride solution is placed in a bath where two inert electrodes are immersed, separated by a selective membrane for cations (Na^+). A generator produces an electric current, then chlorine is formed on the anode ($2\ Cl^- \Longrightarrow Cl_2 + 2\ e^-$), and hydrogen is formed on the cathode, releasing hydroxyl ions ($2\ H_2O + 2\ e^- \Longrightarrow 2\ OH^- + H_2$).

The first chloracne cases were published during the late 19th century, in the context of the development of the German chemical industry. Several companies created in Germany in the 1850s and 1860s became major actors in the chemical industry worldwide: BASF [1861], Hoechst [1862], Bayer [1863], Leopold Casella [1867], Agfa [1873] (Aftalion, 2001). The merging of these companies lead to the creation of IG Farben in1925. Although the first production of chlorine by the electrolysis of brine was attributed to Cruikshank in 1800, the invention of generators of electricity in the 1860s made electrolytic production of chlorine and caustic soda feasible. Electrolysis took place in cells filled with a solution of sodium chloride and immersed in a tank filled with water. The anode was placed in the cell, the cathode in the tank. Chlorine accumulated towards the anode, while sodium ions were transferred to the cathode where hydrogen gas (H_2) and hydroxyl ions (OH^-) accumulated (Figure 11) :

$$2\ NaCl + 2\ H_2O \rightarrow Cl_2 + H_2 + 2\ NaOH$$

The main problem during the electrolysis of NaCl was to achieve continuous separation of chlorine and sodium hydroxide. Charles Watt devised a current-permeable separator which allowed the electric current to pass and kept the anode and cathode products separate. Griesheim Company is credited as the first to use the process commercially for chlorine production, in 1888.

As seen above, the link between the onset of lesions and the exposure of patients to chlorine or chlorinated derivatives was suspected from the earliest observations (B., 1903). All patients examined by Herxheimer were employed in Chemische Fabrik Griesheim [CFG] - Herxheimer did not mention the name of the firm, only Fumouze did – a factory of middle-size founded by Ludwig Baist in 1856 to produce fertilizers and mineral acids (Wagner, 2006). After producing caustic soda from 1859, CFG joined a syndicate of manufacturers in 1884 to exploit a patent for the production of caustic soda and chlorine by electrolysis of salt. Chlorine was converted into chlorinated lime, which was used in large quantities as a disinfectant and for bleaching. The process produced hydrogen, used for heating and filling the Zeppelin airships. CFG also developed a burner for iron welding using a mixture of hydrogen and compressed oxygen. The production unit in CFG, in 1890, was the first in the world for the electrolysis of salt (Wiberg, 2001).

In France, the patients afflicted with chloracne had all been working in the same plant, located in La Motte-Breuil [today Trosly-Breuil], near Compiègne, 50 miles from Paris. At first a soap factory, in 1896, the firm became the "Société industrielle des produits chimiques", one of the most important factories in the area, employing about 300 people ([Anonymous], 1990a). Hallopeau and Lemierre pointed out that it was "the only one in France where chlorine is produced by electrolysis in such large quantities". They suspected that the chloracne that occurred in Herxheimer's patient had a similar origin, due to the indication given by Fumouze that the French factorybelonged to a German firm [Hoechst]. Lehmann confirmed that the French factory was actually a "daughter society" ["Tochter-Etablissement"] of the German firm using the same patent process (Lehmann, 1905b).

Fumouze visited the plant in La Motte-Breuil and published a minute description of the workers occupational environment: "in the room where electrolysis takes place, there are six rows of containers. Twelve cells set inside each container. In each cell are six coal electrodes. […] The twelve cells are arranged in two rows of six. A flat bar is set between the rows. […] The electric current circulates in the bar connected to the cover of the cells on which the electrodes are fixed. […] Sodium chloride is mixed with an odourless and colourless solution that burns the leather of the shoes, and poured into the containers. […] It may be a solution of caustic soda used to initiate the electrolysis. […] The temperature of the liquid in the containers is constantly 70°C. As a consequence, the temperature of the room is always very high […] about 55°C above the containers where the workers have to stay for a while when they change the cells. Once the electric current is running, the sodium chloride is decomposed to caustic soda that emanates from the negative pole and chlorine that emanates from the positive pole, both flowing out throughglass tubes. The tubes are connected to pipes in canvas linked to a pipe exiting from the workshop. The pipes in canvas are supposed to act as safety valves when the pressure of chloride becomes too strong. In this case - that happens every day - the pipes burst which prevent dangerous explosions. In the middle of two rows of cells, above the container and the bars in which the electric current is running, is a footbridge on which the workers can walk. Under the footbridge are two or three holes through

which white hot vapours can outflow. They are made of hydrogen and microscopic globules of salt and caustic soda. They are inflammable; when a cell has to be changed the workers obstruct the holes to avoid an electric spark setting the vapours on fire. […] The workshop is ventilated by windows located only on one side of the room. Only a few of them are opened so that the white vapours can flow outside." *[transl. G. Tilles]*

Of the 200 workers in the French factory, about 15 of them, afflicted with the same cutaneous symptoms [Appendix 1], were involved in the production of chlorine by sodium chloride electrolysis. Fumouze pointed out the particular severity of the disease that affected the workers who changed the cells: "to accomplish that work they have to go up onto the footbridge and are therefore exposed to the hot white vapours […] whereas other workers who remain standing around the containers are less exposed." *[transl. G. Tilles]* The first cutaneous lesions appeared two or three weeks after they entered the plant, whereas other workers were afflicted only five or six months later. Moreover the cutaneous lesions were more intense, especially on the back and genitalia.

Fumouze hypothesized that chlorine was not directly responsible for the dermatosis. He put forward several arguments that, he thought, supported this statement: the workers who have to fix the leaks of chlorine occurring once or twice a day are less afflicted than their colleagues who change the cells; the workers in charge of the collection of chlorinated lime inhale it and are afflicted with severe extra cutaneous symptoms (conjunctivitis, bronchitis, laryngitis, gastritis and frequent vomiting), however they do not exhibit any cutaneous lesion; no description of dermatosis provoked by chlorine has been published since its discovery by Scheele in 1774. Fumouze concluded that the "dermatose chlorique électrolytique" was the consequence of the exposure to sodium hypochlorite originating from the white vapours floating above the containers. Regarding a possible pathogenic mechanism, he suggested that soda hypochlorite forms a "shiny varnish" on the skin surface, irritating the pilosebaceous ostia and obstructing them. Beside this external action, the inhaled sodium hypochlorite "irritates" the sebaceous glands in charge of its excretion. As a consequence of both mechanisms, comedones, sebaceous cysts and nodules form. Finally, Fumouze predicted that the process would certainly be adopted by other factories in Europe, the disease becoming therefore more and more frequent.

Like Fumouze, Thibierge rejected the responsibility of pure chlorine for the dermatosis. He pointed out that the workers exposed to pure chlorine produced in the electrolysis process did not exhibit any cutaneous lesions, which led him to hypothesize that only a chlorinated derivative could be responsible for the disease. He hypothesized that the chemical agent was absorbed through the respiratory or digestive tract. The chemical relationship of chloride with bromide and iodide already regarded as "poisons of sebaceous glands" led Thibierge to suspect that an inhaled or ingested chloride derivative might have a deleterious effect on sebaceous glands (Thibierge and Pagniez, 1900b).

Bettmann, who observed 21 cases of chloracne, also noted that the most of the affected workers were not in involved in hydrochloric acid production but were involved in the cleansing of the towers where hydrochloric gas was absorbed. Chloracne was nevertheless observed in workers in contact with hydrochloric acid in different circumstances [see Wechselmann's presentation of a patient using a solution to clean his hands] (Wechselmann, 1903).

Ho, a Chinese student in Lyon [France] pointed out that workers daily exposed to chlorine were seldom affected by chloracne. Moreover, whereas chlorine was frequently responsible for pulmonary disorders, the workers who suffered from chloracne had no extracutaneous diseases. In fact, wrote Ho, respiratory disorders are absent in chloracne cases that "evolve as a local affection without any alteration of the deep organs." However, as no argument on the origin of the skin disease was really convincing, Ho admitted that "the darkness remained complete" (Ho, 1926).

Jaquet suggested a different pathogenesis model. He rejected sodium hypochlorite as the agent responsible, as proposed by Fumouze, as he failed to find it in comedones or on the epidermis of the workers: "neither chlorine nor sodium hypochlorite can be regarded as the cause of the affection". Visiting the plant where the patients were working, Jaquet observed that the production of a chlorinated derivative was obtained by separating the anode from the cathode in the electrolysis device by the "diaphragm process", a porous membrane that allowed the current to pass (Wiberg, 2001). Jaquet noticed that the most afflicted workers were those in charge of the replacement of the used diaphragms by new ones. To carry out this action, the workers had to break the cement that fixed the diaphragms on the walls. Jaquet therefore hypothesized that the action of the cement on the uncovered skin could be responsible for the disease. In this respect, he rubbed the external ear of rabbits with an ointment containing a mixture of glycerine and cement particles. A few days later, he noticed a "violent inflammation on the ear." Jaquet inferred that cement dust could be the cause of the disease. However, despite these experimental observations, he admitted the possible responsibility of a "concomitant action of a chloride compound" (Jaquet, 1902).

Contrasting with the authors who regarded chlorine or chlorinated derivatives as responsible for acneiform eruptions, others, mainly from Germany, considered chloracne was a tar acne. W. Lehmann, Jacobi's assistant, reported the case of a patient who had been working for eight months in a factory producing electric cables impregnated with a tar-containing mixture. His face was covered with comedones intermixed with sebaceous cysts. Carbuncles were visible on the back and chest. No lesion was noticed on the genitalia (Lehmann, 1905a). Jacobi also suggested the responsibility of tar contained in the electrodes used for the electrolysis process. Habermann quoted Kaposi who also hypothesized that chloracne might be, in fact, the consequence of tar exposure (Habermann, 1933). Rambousek blamed chlorinated tar products given off during the electrolytic manufacture of chlorine by the action of this gas on the carbon anode, made from tar, bitumen and ground charcoal. According to him, the acnes disappeared when the carbon anode was replaced by magnetite (Rambousek, 1913).

Holzmann described two clinical forms of the disease depending on the patients' professional circumstances: when chlorine is produced by electrolysis, the comedones may appear progressively, several months after the beginning of exposure, followed by inflammatory papules and nodules; whereas in the non-electrolysis process of production, the face and hands are first inflamed before the occurrence of comedones and papules 4 to 14 days later. Holzmann asserted that chloracne is more severe than tar acne and lasts longer. Whereas tar acne vanished once the exposure to tar ceased, in chloracne the lesions remained due to the alteration of the sebaceous glands. Finally, concluded Holzmann, chloracne is, anatomically speaking, an acneiform folliculitis and originally a tar acne marked by a usual tendency to inflammation due to the concomitant action of chlorinated derivatives (Holzmann, 1926; Holzmann, 1907). Curschmann, quoted by Ullmann, also pointed out that as "Perna" [see later for Perna Krankheit] was made of chlorine and tar, chloracne had therefore to be regarded as a tar acne (Ullmann, 1922).

Chloronaphthalenes and chlorobiphenyls as causal agents

Synthesized in 1833, chloronaphthalenes were patented in the US in 1909. In 1900, Aylsworth [US] noted that the properties of chloronaphthalenes - clinical inertness, a high dielectric constant, low viscosity close to the melting point and fungicidal and insecticidal properties - could be highly profitable in industrial processes (Crow, 1970).

The “Perna Krankheit”

In this respect, during World War I, due to the difficulties in obtaining resin and rubber, in Germany clothes and gas masks were waterproofed by impregnation with PERchlorinated NAphthalene - designated as Perna - i.e. chlorinated naphthalene in which eight of the hydrogen atoms are replaced with chlorine (Schwartz, 1936). Wauer [Berlin] was probably the first to publish the occurrence of comedones and sebaceous cysts among the workers who manipulated hot naphthalene. He coined the name of the disease from the name of its causative agent, “Perna Krankheit” (Wauer, 1918). After the conflict, chlorinated naphthalenes were no longer used to impregnate clothes, but were still used to isolate electric cables and wicks used in coal mines. Several cases of chloracne were observed.

Teleky?described 33 severe forms of chloracne, 37 moderate cases, 38 light cases and 62 women who had negligible symptoms). The eruptions mainly occurred in workers in charge of the impregnation of electric cables with Perna. A few cases were also noticed in workers in charge of winding the cables. The lesions first appeared on the temples in a triangular area close to the external angle of the eyes then extended to the cheeks. In the most severe cases, the face, nape of the neck and neck were speckled with a great number of papules the size of a grain of millet, with small nodules and with comedones between the nodules. Teleky did not notice the grey or dark colour previously observed. He remarked that the mixture handled by patients afflicted by chloracne contained from 23% to 60% chlorine. In a plant where chloracne was almost absent, the mixture contained only 14% chlorine. Teleky inferred that Perna must not contain more than 15% chlorine to avoid the onset of the cutaneous disease; he also suggested that the room where the impregnation took place should be properly ventilated and the various stages for the completion of the cables

should be carried out in separate rooms. A few years later, Teleky changed his mind and suggested that the chlorine concentration was not responsible for the disease but a volatile chlorinated derivative was more likely the causal agent (Teleky, 1927b; Teleky, 1927a; Teleky, 1928). Additional cases of "Perna Krankheit" were described in the 1930s and 1940s (Holzmann, 1937; Winkler, 1950). In 1949, Teleky reported he had seen between 150 and 200 workers with the disease, sometimes preceded by nausea and oedema of the face and hands. According to him, a liver disease could occur independently from chloracne, four to six months after exposure or earlier. Autopsies in these cases revealed yellow atrophy of the liver (Teleky, 1949).

Broussolle published a paper concerning two patients hospitalized at Hôpital Saint-Louis. The face of the first one was partially covered by black dots mimicking a tattoo or "gun powder shot from a short distance". The legs, thighs, forearms and dorsal aspect of several fingers also exhibited comedones. The second patient presented a mild form of the same disease with only few comedones on the malar crescents. Visiting the plant where these two workers were employed, Broussolle could see five additional male patients affected with similar cutaneous lesions. All of them were working in the factory producing naphthalene from coal tar (Broussolle, 1919).

In the 1920s, Nicolas, Pillon and Lacassagne [Lyon, France] published three cases of "acné chlorique" (Nicolas and Lacassagne, 1929; Nicolas and Pillon, 1925). They pointed out the fact that the only men affected were those who worked close to coal and pitch. According to Sisley, a chemist working with them, many combinations could occur with pitch resulting in the formation of 2,3,8 trichloronaphthalene which, he thought, was responsible for chloracne and would also explain the black colour of comedones (Nicolas and Pillon, 1926). The confirmation of its responsibility was obtained by two experiments conducted by Nicolas and Pillon: trichloronaphthalene under an occlusive dressing was applied on a 10 cm^2 area of the back of a patient. A few hours later, they observed on the applied area an erythema so intense that they decided to stop the experiment. On the fourth day, an eruption looking like acne vulgaris was present on the applied area with so many comedones that the skin had the appearance of a rasp. The same chemical was applied on a similar surface of the chest of another patient. A day later, an intense erythema was also observed. Two days later, the surface was entirely covered with tiny black points looking like a tattoo. The authors kept the applications on and four days later the area had become brown-red as though chrysophanic acid had been applied to it. The same chemical was also applied to a similar skin surface on the back. An acne appeared five days later, as in the first patient. The black points were numerous, the pressure of which led to the extraction of typical comedones, intermixed with papules and pustules. The authors concluded that chloronaphthalene coming from the chlorine-coal tar combination in the electrodes was noxious for workers and responsible for chloracne.

The 1930s to 1950s outbreak

Whereas a limited number of cases were published up to the 1920s, from the 1930s to the 1950s, chloracne cases became so numerous that some physicians even spoke of an industrial outbreak. Moreover, a few observations showed that workers affected by chloracne exhibited not only a benign cutaneous disease - although disfiguring in some cases - but that they could also suffer more serious diseases some of them fatal. In this respect, concerns about the toxicity of chlorinated derivatives increased and the value of chloracne as the hallmark of systemic poisoning was suspected although the causal agent was not yet clearly identified.

First steps of an industrial "epidemic"

On January 19, 1934, Courtois-Suffit et al. [Paris] examined six women working in the same plant and all affected by a skin disease they named "acné comédon". After investigation in the factory, it was revealed that, of 56 workers, 50 had cutaneous diseases. More than 20% of the affected patients had had oedematous erythema sometimes followed by acute eczema. Thirty-two workers had typical chloracne mainly on exposed cutaneous areas. None had melanoderma. Thirteen of them had slight general symptoms, such as nausea or loss of appetite. According to the authors, the cutaneous lesions resulted from the direct action of chloronaphthalene fumes on uncovered areas of skin. They suggested, however, that particles of pitch added to trichloronaphthalene might be partly responsible for the cutaneous lesions. The authors stressed the need to ventilate the plant, to provide the workers with long-sleeved clothes and to ensure proper cleaning as prophylactic measures (Courtois-Suffit *et al.*, 1934; Touraine *et al.*, 1934). Commenting on the work of his colleagues, Duvoir [Paris] suggested that the severity of the lesions might be the consequence of the combined action of tar and chlorine (Duvoir, 1934).

Two years later, still in Paris, Burnier reported an "epidemic" of chloracne among 12 employees of a radio factory in which Haftax® - wax made from chlorinated naphthalene produced in Germany - had been employed for six months before the onset of the disease. During the melting of the wax, heavy black vapours were produced. The workers in charge of the melting process carried liquid wax into a different room in the plant where it was kept at 120°C. Workers dipped electric capacitors in the hot wax so that they were insulated by impregnation with chlorinated naphthalene; other workers handled cold capacitors. Two months after exposure to Haftax®, all workers either exposed to hot wax or manipulating cold capacitors complained of headaches, fatigue and nausea that preceded the appearance of cutaneous lesions: folliculitis, brownish pillar keratosis or "acné comédon" located on the forehead, cheeks, the posterior aspects of the earlobes and sometimes on the neck. Following Burnier's presentation, Touraine reported 20 additional cases of chloracne occurring in the same plant as the patients observed two years before (Burnier, 1936).

Due to the fact that on July 12, 1936, “acne” caused by trichloronaphthalene had been added to the list of occupational diseases for which compensation could be obtained, cases of chloracne progressively diminished in France. Only a few cases were still observed in Paris involving employees who had been working in Germany during World War II. For instance, in 1945, Touraine and Ruel reported the occurrence of intense chloracne on two repatriated French prisoners, who had been working in a German plant making capacitors (Touraine and Ruel, 1945). In Germany, in the same period, Fuss, Flury and Zernik also described acne-like eruptions due to chloronaphthalene manufacturing, occurring on uncovered parts of the body and covered parts (in case of friction) (Flury and Zernik, 1931; Fuss, 1937).

In London, after seeing a man aged 28, whose job consisted mainly in putting up circuits of flame-proof wire, affected by many blackheads on his face, Haldin-Davis was able to examine eleven employees working at Victoria Station engaged in similar occupational activities. Nine of them exhibited blackheads on their foreheads, on the nape of the neck and on their forearms. All these workers were employed “indoors in pulling wire covered with chlorinated naphthalene through conduits which were above their heads and this process resulted in the detachment of fine particles of the coating which fell on their heads and necks”. Haldin-Davis hypothesized that the skin disease was actually caused by the fine dust and not by an exhalation of the chlorinated naphthalene (Haldin-Davis, 1939).

Then, the higher chlorinated derivatives - more resistant to heat and more waterproof –- became extensively used whenever resistance to heat and moisture was necessary: in boat hull coatings (notably during the war period because of their antimagnetic properties), in electronics, in the radio and television industries as insulating waxes, sealing compounds and dielectrics for condensers, as high pressure additives for lubricants, as wood preservatives and in paints, varnishes and lacquers.

In the US, although cases of chloracne in workers exposed to synthetic waxes had been observed in 1912 (Taylor, 1974), a great number of cases appeared in the 1930s in employees manipulating electric cables. There were so many that the disease was also named “cable rash” or “electricians rash” or “Halowax® acne” - for HALOgen wax- referring to the trade mark of the causative substance. Halowax® manufactured by a subsidiary of Union Carbide and Carbon Company was a mixture of chlorinated hydrocarbons produced chemically by chlorination of naphthalene and biphenyl.

In 1936, Fulton and Matthews reported patients exhibiting dermatitis occurring in a wire insulating plant in Pennsylvania. They also mentioned that besides the patients, members of their families were afflicted, probably through contact with the clothing worn by the workers in the factory (Fulton and Matthews, 1936).

Mayers and Silverberg observed three types of dermatosis in 31 workers engaged in two plants in which a mixture of tri- and tetrachloronaphthalene was used in impregnating electrical condensers,: acneiform eruption, vesiculo-erythematous eruption and simple erythematous eruption

with pruritus. All afflicted employees were working in the “finishing department” where exposure to chloronaphthalene resulted from flaming the impregnated condensers, causing a volatilization of the wax. The period of employment before the first cutaneous signs appeared varied from a few weeks to less than 18 months. Among the 31 patients, 6 of them [4 females and 2 males] exhibited severe lesions “mostly pinpoint to pea size, yellow, white or slightly pinkish papules, often distinctly per follicular and surrounding large comedones. Sometimes an area of closely packed large comedones could be seen without any surrounding reaction. This gave the skin a black spotty appearance.” Mayers and Silverberg insisted on the (value / importance) of pruritus, which they considered as “not greatly stressed in the literature as a whole.” The workers themselves were especially concerned about the comedones and the itching and characterized the rash “as the blackhead itch”. The authors also observed four mild cases of acneiform eruptions, regarded as not significant, made of a few pinpoint papules or scattered comedones on the face, around the elbows and on the extensor surfaces of the arms. In fact, the eruption was so mild that Mayers and Silverberg hesitated to make a definite diagnosis. Whatever their severity, the lesions were mainly located on the forehead, cheeks, chin and “the line along the mandible”. The nose was always spared. The rash tended to vanish two or three months after the exposure ceased. All patch tests with chlorinated naphthalenes performed on patients suffering from acneiform eruptions were negative (Mayers and Silverberg, 1938). In an overview of chloracne, ?Crow? suggested that the coexistent presence of vesicular dermatitis mentioned by Mayers and Silverberg supported the role of pitch (Crow, 1970).

Chloracne, “sentinel event” of systemic toxicity

To the best of our knowledge, the first cases of hepatotoxicity in workers exposed to chlorinated naphthalenes - heated above the melting point and giving off fumes - were published in 1936 by Flinn and Jarvik. Three men working in three separate plants were affected with yellow atrophy of the liver. The patients were actually exposed to different compounds: a mixture of tri- and tetrachloronaphthalene [compound A], a mixture of tri, tetra- and pentachloronaphthalene [compound B], and a mixture of penta- and hexachloronaphthalene [compound C]. After injections on rabbits, death occurred with compounds B and C. The authors inferred that chloronaphthalene might be the cause of the yellow atrophy of the liver (Flinn and Jarvik, 1936).

Following these observations, in the spring of 1936, Drinker [Harvard Medical School] was asked by Halowax Corporation to investigate whether chlorinated naphthalenes [tetra- to hexachlorinated] and chlorinated biphenyls were responsible for the deaths of the employees. Drinker presented his results in 1937 at a Harvard meeting attended by representatives from Monsanto, General Electric, Halowax, the US Public Health Service and health officials from Connecticut and Massachusetts. After reviewing the “meagre literature” on the subject, Drinker concluded that, except for the observation published by Flinn and Jarvik, there were no reports of

these substances having a serious effect on humans. He underlined the absence of published figures on the amounts of chlorinated naphthalenes in the air which will produce injury of any sort.

After experimenting with chloronaphthalenes toxicity on white rats, he stated that “compounds more highly chlorinated than trichloronaphthalene are capable of causing liver injury when inhaled steadily in quite low concentrations.” He regarded chlorinated biphenyl as “certainly capable of doing harm in very low concentrations and [is] probably the most dangerous.” Drinker concluded that “the experiments leave no doubt as to the possibility of systemic effects from the chlorinated naphthalenes and chlorinated biphenyls. […] The degree of chlorination seems to determine the systemic toxicity […] the compounds tested attack the liver and the liver alone.” Drinker pointed out the “extraordinary thing that even the most searching examination fails to show injury in any other region”. As for prevention, the authors stressed the importance of the ventilation of the workrooms so that “the air breathed does not contain more than 0.5 per cubic meter of any of these compounds above trichloronaphthalene.” Following Drinker’s presentation, attendees expressed divergent opinions on the actual responsibility of the substances, the sanitary consequences and the proper preventive measures.

Sanford Brown, President of Halowax Corporation, underlined the large number of users of chloronaphthalenes before serious adverse effects occurred: “it has been on the market for 25 years. Until within the past four or five years there has never been any intimation that it would cause any systemic effects. Thousands and thousands of workmen have dealt with millions of pounds of certain of these materials particularly the trichloronaphthalene. Then we come to the higher stages combined with chlorinated biphenyl and suddenly this problem is presented to us.” In this context, he also tried to mitigate the responsibility of his company as, he wrote, “we had asked various authorities interested in public health, going back over a period of 15 to 20 years to investigate it but there wasn’t much enthusiasm. […] Now so far as these changes are concerned, they are beyond our control to a certain extent.”

Vosburgh, Medical Director, General Electric Company, pointed out the fact that cables and wires impregnated by chloronaphthalenes are not always used in proper conditions : “we have also customers who use wires and cables in tunnels, in enclosed spaces, splicing them together. I am not certain that we know what the concentration of these chlorinated hydrocarbons is under those conditions.”

Kaimer [York Wireworks, General Electric Co] reported his experience with chloracne cases: “One and a half years ago there were 50 to 60 men afflicted by various degrees of this acne about which you all know. Eight or ten of them were very severely afflicted - horrible specimens as far as their skin condition was concerned. One man died and the diagnosis may have attributed his death to the exposure to Halowax vapours but we are not sure of that. […] More serious than that perhaps is the fact that we had 50 other men in very bad condition as far as the acne was concerned. […] The first reaction of several of our executives had was to throw it out - get it out of our plant. But that was easily said but not so easily done. We might just as well have thrown our business to the

four winds and said, 'We'll close up', because there was no substitute and there is none today in spite of all the efforts we have made through our own research laboratories to find one."

Then Kaimer emphasized the sanitary measures put in place in the York plant “for bringing these men to normal health condition. […] A number of them were sent to […] the University of Pennsylvania hospital and to Johns Hopkins. […] We employed a trained nurse and two local physicians and you might say established a small hospital and its facilities at the plant. […] We have in this year and a half brought each and every man back to normal skin condition. […] With the adequate ventilation system we have installed, with the routine for change of clothing from street clothing to work clothing when they come to work and the reverse of that process, with an assurance a shower will be taken before the street clothing is again put on, we have found no recurrence of skin trouble. Each and every man working with Halowax products […] is examined twice yearly.”

Schwartz, Medical Director, Dermatoses Investigations, US Public Health Services, New York] underlined the value of chloracne as a marker of the efficiency of the ventilation systems and of systemic toxicity: “while we cannot with our present knowledge, detect by any chemical tests the early symptoms of intoxication from this substance [Halowax], the skin offers an easy way of proving whether your method of ventilation is efficient or not. If there are any cases of acne or of this dermatitis occurring in a plant where Halowax or the chlorinated naphthalenes or chlorinated biphenyls are used, then that shows that there is sufficient concentration of these substances in the air to cause plugging of the follicles and to cause a skin condition. If there is sufficient concentration to do that there may be sufficient concentration to cause systemic poisoning in the few people who are hypersensitive to the action of these hydrocarbons.” Sanford Brown concluded the meeting by stressing the “necessity of not creating mob hysteria on the part of workmen in the plants” (Drinker *et al.*, 1937; Francis, 1994).

Despite the preventive actions supported by the attendees at this meeting, additional cases of chloracne were observed, some of them with systemic symptoms leading to death. Two years later, Drinker had to admit that the recommendations “as to safe concentrations in the air of the workroom” he published two years before, “had not progressed far enough to merit description.” He presented a complementary list of 14 chlorinated hydrocarbons with chlorine contents and permissible limits for the air in the workrooms (Drinker, 1939).

In 1939, Greenburg et al reported in detail the cases of three young people who died from hepatic disease. The first patient seen at the Lindbergh Hospital in New York City presented the typical features of this fatal disease: “ A girl aged 17 was admitted on April 26, 1932, in a semi-comatous condition. The occupational history was as follows: she obtained a job with a concern manufacturing electrical condensers for use in radios. She worked at this one place for seven months and stopped working there seven days before her admission to the hospital. Her work consisted in soldering and labelling condensers. She may have also assisted in the sealing operations. In the soldering of the condensers, she was exposed to the fumes of tri- and

tetrachloronaphthalene with which the condensers were originally impregnated. The present illness began about five months before admission to the hospital, when she noted several pigmented areas on her face. She was referred to the skin clinic where a diagnosis of acute catarrhal jaundice was made. A diffuse papulopustular eruption was present on her face. Some of her co-workers were also suffering from a similar acneiform eruption. The patient gave the impression of being a coloured girl although she was in reality white. There was general puffiness of the face, hands, feet and abdomen. The first admission note stated the "patient is so jaundiced that her face is black". A careful examination revealed a (negroid type of pigmentation?). There were three areas somewhat darker than the rest, appearing very much like dabs of charcoal - one on each cheek below the eyes and one on the chin. On close examination these spots appeared to be the result of aggregations of comedones. Over the skin of the abdomen there was a girdle-like area of deeper pigmentation beginning at the level of the umbilicus and extending to the pelvis. The patient presented a picture which was puzzling to all physicians who saw her and a non-conclusive diagnosis was reached at the time. The clinical course was steadily down-hill. At 11pm on April 27, the patient became unconscious and went into a coma. On April 28, the patient died. The autopsy revealed a typical picture of clear subacute yellow atrophy of the liver. "The toxin had destroyed evidently most of the liver cells. It has been one or more attacks of hepatitis judging from the different ages of the pathological process in various parts of the liver". The clinical report concluded that "an unknown toxin has evidently caused a severe diffuse cytolysis involving most organs predominately the liver".

A careful examination of these three people failed to find any predisposing cause for the hepatotoxicity. The authors admitted it was impossible to say whether the hepatic lesions were the result of primary intoxication or merely secondary to liver damage. They favoured however the latter. They pointed out the occurrence of the cutaneous lesions in the first case "aggregations of comedones", "characteristic of the dermatitis provoked by chlorinated naphthalenes", prior to the systemic symptoms. However they admitted that the "question as to whether or not the skin eruption in such a case is in any way connected with the onset of systemic effects cannot be answered since no correlation has been established thus far between skin lesions and systemic disease." Due to the severity of the clinical pictures that ended by death, Greenburg et al. strongly recommended careful medical control, notably the occurrence of acneiform eruption as a sentinel event and "conscientious reporting by physicians of all illnesses occurring among workers exposed to the chlorinated naphthalenes and biphenyls. […] persons suffering from the acneiform eruptions should be removed from further exposure. Persons who have had any liver disease should not work with these substances". Finally, the authors supposed that if "the girl had been promptly removed from further exposure […] it is possible that her life would have been saved" (Greenburg *et al.*, 1939).

Collier observed 12 cases of chloracne that occurred during September and October 1941. Among the workers who had chloracne, one died from yellow atrophy of the liver. Collier reported

a case history, actually similar to those previously published in the US: “For three to four months before the onset of these cases, there had been technical difficulties about getting efficient exhaust ventilation for the fumes rising from the bath in which the chlorinated naphthalene was being melted. […] A woman of 41, started working in the chromium plating department. […] on June 9, 1941. […] She never came in very close proximity to the fumes of the melted chlorinated naphthalene wax. […] However she was seated 15 feet from the bath and worked there during the whole of the time of the technical difficulties in constructing efficient exhaust ventilation for the fumes coming from the bath. […] She ceased work on December 26. […] She was admitted on January 17, 1942. […] Four and a half weeks before admission she was becoming slightly jaundiced. […] On January 20 […] about noon she became unconscious. […] All the time, the liver dullness was decreasing, until no dullness could be detected on January 22, when she died. […] Histological examination showed acute yellow liver atrophy” (Collier, 1943). Collier mentioned that in a Home Office Memorandum [1941] on poisoning by chlorinated naphthalene, two cases of jaundice were mentioned, one in 1935 and another in 1938. He also reported two additional deaths of workers in different factories and two others in November 1940 and January 1941. In April 1941, the mounting evidence of chloronaphthalenes toxicity incited the Home Office [UK] to extend the list of industrial diseases under the Workmen’s Compensation Act to include poisoning by chlorinated naphthalene or its sequelae.

Reviewing chloracne, Schulz [Hamburg], although pointing to myocardial, kidney, pancreatic and stomach alterations, regarded liver toxicity as the main systemic effect (Schulz, 1968).

Additional cases of chloronaphthalene toxicity. Outbreak in the US Navy

In 1934, Sulzberger et al. published observations on three workers - two men and a women - who had “acne of the face, forehead, cheeks, chest and back”. According to the authors, these cases illustrated the clinical results of a substance that caused “irritation of the pilosebaceous apparatus” (Sulzberger and Rostenberg, 1934).

Thelwell-Jones, a physician employed by ICI [General Chemicals], published the results of a survey of almost 3,000 workers he had the opportunity to examine from 1935 to 1941 (Thelwell-Jones, 1941). Of these, 359 workers developed various skin diseases [impetigo, eczema, irritating dermatitis, psoriasis] and 169 of them - i.e. 47% of total skin diseases - were afflicted by chloracne. The latent period varied from one month to two years. Thelwell-Jones described in detail two cases he regarded as the “most severe, and illustrating many typical features of the disease”:

“A.C. aged 43 years, commenced work in 1932 as a pipefitter and, in January 1933, began work on a process using molten chloronaphthalenes in an open vessel. The condition commenced in April 1933 as “pimples” on the lower part of both arms and between the legs. Loss of rest due to the irritation of the skin. Itching very marked. The face shows a few comedones only. Comedones are very numerous on the neck and extend slightly into the hair but infection is slight. Few comedones

with slight infection are present behind the ears and under the chin. The comedones are numerous upon the chest. The breasts are especially affected with large follicles. Secondary infection is prevalent upon the upper abdomen and comedones are numerous upon the back, especially in the lumbar region. Comedones are very numerous upon the arms and many are infected. The upper part of the thighs, the scrotum and the penis have many infected follicles. Removed from work with chlorinated naphthalenes in January 1934. Improvement commenced on the face, back and arms. Lesions on the chest persisted up to November 1935."

"T.J. aged 25 years. The acne commenced in March 1933; latent period, two months. The irritation was marked especially when he became warm. Pimples appeared on the lower part of the back and stomach and spread to the back, arms, face, back of head, legs and scrotum. The skin is normal between the lesions and there is no alteration in pigmentation of skin elsewhere. Practically the whole body is affected with comedones but infected follicles are few. The scalp is free. Slow but steady progress was made after removal from the process. Many blackheads remained on the face until March 1934. Numerous blackheads were present on the buttocks until August 1937."

Due to the fact that 45% of the 81 workers exposed to fumes became affected by chloracne, Thelwell-Jones inferred that "acne has been produced under conditions of exposure to the fumes of heated chlorinated naphthalenes. […] No case of acne has arisen from handling the cold products although approximately 50 men have been exposed to this risk. […] The conditions necessary for the production of acne are that the chloronaphthalene shall be present in a finely divided state. This may occur when the products are volatilised by heating or are present in a solution which is allowed to evaporate or as dust. […] employees exposed to constituent products do not contract acne. Thus no cases of acne have arisen during the manufacture and use of chlorine".

Like previous authors, Thelwell-Jones quoted the observation of an acneiform eruption occurring on an infant aged two and a half, affecting the cheeks, forehead and extensor surfaces of arms and forearms. The father, exposed to hexachloronaphthalene and biphenyl, had developed chloracne. The mother was affected on the buttocks, cheeks and thighs and the sister aged eleven months had comedones on both cheeks. The father returned home in his soiled working clothes, played with the child without changing, and slept with his son. Thelwell-Jones suggested that the probable mechanism of production is that chlorinated naphthalenes are deposited on the skin and clothes in fine particles and as they are liposoluble, they are dissolved in the sebum. In the absence of cleanliness, the chloronaphthalenes irritate the sebaceous glands, causing an excess of cell growth and secretion, followed by plugging of the gland and secondary infection (Fulton and Matthews, 1936). Finally, regarding the pathogenesis, Thelwell-Jones admitted that it was unknown "whether the effect is a local one or arises from the absorption of the product into the body".

Good and Pensky described cases of cutaneous disease that occurred in electricians. Heat was rarely used and the exposure to fumes was quite rare. The authors noted, however, that all workers [52] handling cables had various degrees of "cable rash" made of "large comedones [that] appear in the follicular orifices as a result of the activity of the follicle. […] These comedone-like lesions are

found in almost countless numbers on the exposed portions of the body, especially on the face and forearms. […] The most frequent sites […] were on the skin over the malar eminences, the circumorbital areas, the margins of the lobes of the ears and the mastoid regions. […] The skin of the nose was rarely affected." The latent period varied from a few weeks to several months. A few workers' wives had slight eruptions resembling their husbands' (Good and Pensky, 1943). Beside the skin lesions, the affected workers complained of extracutaneous symptoms: nausea, loss of appetite, headaches, alopecia, loss of weight. However no systemic disturbance was observed that could be related to the exposure to chloronaphthalene. Various keratolytics, soaps, antiseptics and (Roentgen therapy "in careful dosage" were used as treatments. In a few patients, the eruption persisted as long as one and one-half years after the exposure to the causative agent had been discontinued. Prophylactic measures were obviously promoted: rigid cleanliness of the skin as well as the reduction of Halowax® concentration in the worker's environment, frequent changing of clothes, ventilation of the working spaces, use of protective creams, of protective clothing devices [masks, sleeves and trousers] and the use of chemical neutralizers against Halowax® - named "penetrasols"- that coudl penetrate into the hair follicles and ducts of the cutaneous glands (Herrmann *et al.*, 1942).

Regarding the pathogeny, the authors rejected the possibility of a hypersensitivity due to the negative results of patch tests. They hypothesized that the eruption could be the consequence of a foreign-body reaction in the hair follicles and sebaceous glands due to the mechanical plugging by the particle of chlorinated naphthalene and from the condensation of the fumes emitted from the waxes in the cables.

In the US, during WWII, due to the shortage of the usual electric insulators, halogenated waxes were extensively used. US Navy workers were exposed to Halowax®, either dust or fumes, when working on electric connections in confined spaces, notably in boats under construction. As the number of chloracne cases increased, mainly affecting young men who were more susceptible to develop "acne rash", it was suggested that "older employees should be used whenever possible in installing cables. Exhaust ventilation should be used to catch the fumes and small flakes of chlorinated wax. Protective ointments should be applied to the hands, face, neck and other exposed parts. […] Separate lockers should be supplied for street clothes and working clothes. Street clothes should never be worn at work. […] Daily shower baths should be compulsory after work.[…] Work clothes should be changed daily.[…] Avoid as far as possible all contact of skin with the material. […] Do not use wiping rags for the nose and face" (Connelly and Marsh, 1944).

Despite these preventive measures, cases of chloracne were still observed as in the US Navy due to the entrance of the US into the war, as underlined by Schwartz, who noted that the "speed-up in our shipyards had in many instances resulted in failure to install the proper safety precautions necessary when handling wires insulated with these substances." Due to the lack of precautions and the "speed-up", numerous cases of chloracne among electricians installing cables were reported to the US Public Health Service. Moreover, as deaths had already occurred in the plant where the

wires with which the electricians worked were made, chloracne and the possible systemic effects of chloronaphthalenes became an obvious matter of concern. In this context, a representative of the US Public Health Service was in charge of giving the workers and the unions proper information. The four shipyards where the "cable rash" was reported were visited. The investigators came to the conclusion that the constant handling of cables in which Halowax® was loosely packed and flaked off, was responsible for the acne that occurred mainly among the "strippers" due to the fact that Halowax was impregnated into the asbestos wrapped around the wires as insulation. A list of recommendations was given for those workers who spent most of their day "stripping" cables: they should be supplied with hood respirators, e given clean coveralls daily, wear long underclothes daily laundered, take showers before leaving the work place and use a protective cream provided by the US health service (Schwartz, 1943).

Also in relation to the US Navy, Cotter studied the adverse effects of pentachlorinated naphthalenes on workers engaged in manufacturing cables. He found seven cases of men who developed systemic symptoms; nausea, dyspnoea, loss of appetite and jaundice. No patient exhibited typical chloracne. The most constant early symptom was described as a "papular rash of the exposed surfaces in white men and a corresponding depigmentation" in black men. Two workers died, six to ten months after the onset of the exposure. The autopsies showed in some areas of the liver "a complete absence of liver cells […] the central portions of the lobules were haemorrhagic […] no liver regeneration in the areas lacking any parenchyma.[…] Elsewhere there was only partial loss of liver cells and those remaining had proliferated to form nodules without the usual lobule architecture". Regarding the pathogeny and prevention, Cotter considered that "under the exigencies of war it [was] not possible to relegate such problems to the field of time-consuming research. No factory engaged in a war contract can suspend operations even for an hour. Workmen cannot be transferred or laid off in numbers which interfere with production schedules and must be studied on the job as humanly as possible" (Cotter, 1944).

Kelley reported 55 additional cases of chloracne, occurring from September 17, 1941 to January 1, 1943, among 200 workers exposed to the fumes of chlorinated naphthalene used as an insulator and described briefly the occupational conditions of the employees: "during the process of insulation the wax is heated and much of it vaporizes. The operator and those nearby are exposed to the vapour which eventually solidifies on cooling and as a result small particles adhere to the exposed skin and to the work clothes through which it penetrates to the covered skin. After weeks or months of exposure to the vapours or the handling of the cold product, much of the wax enters the follicle due to rubbing, friction of the clothes or during the process of bathing." The time of exposure before the appearance of the first cutaneous lesions varied from five days to eight months. There were so many comedones on the faces of the affected workers that in some cases they produced an appearance of pigmentation. Kelley confirmed a previously noted "common finding : grouping of countless numbers of comedones of about pin-hole size on the zygomatic areas giving the appearance of 'black eyes' at a distance. In other areas they were larger. These differed from the

comedones of acne vulgaris in that they were darker, more numerous and were itchy". Repeated patch tests with Halowax® were negative. To take care of the workers, they were removed from contact with Halowax® before being treated with X-ray therapy as in the treatment of acne vulgaris (Kelley, 1943).

Peck, from the US Public Health Service [Bethesda], stressed the increased incidence of the so-called chloracne that affected not only almost every worker sufficiently exposed for a few months to chlorinated compounds, but also the family members, in the case of contact with soiled clothes. He also confirmed that chlorine itself was not responsible for the skin disease neither by contact nor by oral administration. Only the highly viscous chlorinated hydrocarbons could cause chloracne. Moreover, underlined Peck, chloronaphthalenes associated with chlorodiphenols in the composition of Halowax® "not only cause lesions of the skin but give rise to acute yellow atrophy of the liver". He suspected that the lesions were due to chlorinated compounds deposited on the skin from fumes and solution. Once deposited, the compounds plug the orifices and exert a keratogenic action that causes the comedones. The obstruction of the mouth of the sebaceous glands and the keratinization of their walls then give rise to the cysts. Peck also described the main pathological feature of chloracne as large sebaceous cysts filled with keratinous material and little sebaceous matter. Due to the increasing use of chlorine compounds Public Health Officers organized teaching sessions for dermatologists so that they could become acquainted with the clinical differences between acne vulgaris and the so-called chloracne (Peck, 1944).

Several cases of chloracne were presented at the meeting of the Royal Society of Medicine [section of dermatology] on January 20, 1944. Two girls employed for 18 months in a condenser-manufacturing factory, in close proximity to heated, molten See-kay® wax [chlorinated naphthalene resembling Halowax®] (Grimmer, 1954; Höfs, 1950; Schulz, 1957) exhibited a great number of comedones on their cheeks and earlobes. A participating physician indicated he had the opportunity to examine 120 girls who presented with chloracne while working in a similar environment. One of the patients died from acute yellow atrophy of the liver. A third participant, who visited a factory engaged in plating for torpedo boats where waxes were used, indicated that the proportion of badly marked workers was about 20%. All physicians suggested that chloracne was due to the fumes arising from molten wax. Workers could benefit from compensation under the Workmen's Compensation Order 1941 (Wigley, 1944).

In Belgium, Dussart [Anvers] observed 56 cases of chloracne among 150 employees in a plant manufacturing paper capacitors (Dussart, 1947a). Several months later, Dussart presented a boy aged eight from Basel where an epidemic of chloracne had occurred, mainly among children (Dussart, 1947b).

In Spain, Contreras observed 58 cases of chloracne limited to the exposed skin of workers handling electric cables (Contreras, 1950). From 1950 to 1959, more than 300 cases of chloracne were reported in Germany in workers exposed to chloronaphthalenes and chlorobiphenyls used for

Nibrenwachs® - produced by Bayer and named after its physical property [NIcht BRENnend]- a material similar to Halowax .

Grimmer [Berlin] reported 60 cases of chloracne in workers exposed to chlorinated naphthalenes. He noted the evolution of the disease fell into in two stages, which is not encountered in acne vulgaris: the first stage was acute and consisted of erythema and oedema, looking like photodermatosis; the second stage was chronic and monomorphic, characterized by comedones. Besides the workers, family members were also "contaminated" exhibiting light forms of chloracne. Finally, after reviewing 14 fatal cases, Grimmer emphasized the toxicity of chloronaphthalenes (Grimmer, 1955). Braun [Heidelberg] reported 123 cases (114 females and 9 males) working in a factory making condensers. Braun noticed that, besides the patients, two husbands and one child exhibited chloracne lesions on their faces. He regarded the lesions as the consequence of skin to skin contact (Braun, 1959).

Occupational exposure to polychlorinated biphenyls

Close to chloronaphthalenes in their chemical inertness and resistance to oxidation and their insulating ability and flame proofing qualities, polychlorinated biphenyls [PCB] were synthesized in 1881 by Schmidt and Schutz. They were first manufactured in 1927, by the Anniston Ordnance Company which became Swann Chemical Company, which was purchased in 1935 from the Monsanto Industrial Chemical Company. Monsanto produced PCBs at plants in Sauget, Illinois and Anniston, Alabama until 1997 ([Anonymous], 2017; Grunwald, 2002).

PCBs were actually little used until 1930 when the Westinghouse Company discovered their advantage over mineral oils in the manufacture of high voltage paper capacitors (Crow, 1970). They were extensively employed during WWII as they replaced substances that were more flammable, less stable and bulkier for the production of safer electrical equipment, mainly capacitors and transformers. They also became extensively used as heat-transfer fluids in heat exchangers, as hydraulic fluids, as ingredients in plastic, paints, adhesives, lubricants, carbonless copy paper and immersion oil for microscopes ([Anonymous], 1978b).

About 58 trade names were used for PCBs and PCB-containing products. Among them the PCB mixture manufactured by Monsanto commercialised under the name Aroclor® was probably the most widely used as an insulator for automobile electric wires, in capacitors, and as a delusterer of rayon (Koppe and Keys, 2002). It could also be found in synthetic resins, synthetic and natural rubbers, cellulose resins, paint varnish, wax, asphalt and ally starch as well as being employed for dust prevention, moisture proofing, sealing and impregnation. Aroclor® products were assigned numbers depending on the amount of chlorine they contained. For instance, Aroclor® 1260 contained 60% chlorine whereas Aroclor® 1242 contained 42% chlorine (Kimbrough, 1972).

The number of uses of PCBs increased to such an extent that, between 1929 and 1988, the total world production of PCBs was 1.5 million tonnes, excluding China and the USSR (Koppe and

Keys, 2002). From 1954 to 1984, 600,000 tonnes were made in the US (Stringer and Johnston, 2001).

The first cases of chloracne associated with chlorinated biphenyls were published on May 2, 1935 by Jones and Alden, who made a presentation at the 58th Annual Meeting of the American Dermatological Association, on an outbreak of chloracne in a factory manufacturing chlorinated biphenyls. Twenty-three workers were affected. The most typical case was a 26-year-old black man, who "began work in the distillation of chlorinated biphenyl in April 1930 […] About May 1933, he noticed the appearance of blackheads on his face, neck, arms and legs. […] Many of these blackheads swelled and became infected." The patient exhibited "a peculiar peppering of the skin with tenacious carbon-coloured comedones (which) was apparent around the umbilicus and lower portion of the abdomen. The scrotum and penis were affected in a similar process". The authors concluded that the "whole eruption was acneiform but differed from acne particularly in the lack of a seborrheic appearance of the skin and in the peculiarly deep black of the comedones as well as the general peppered distribution in areas not usually involved in acne vulgaris." Regarding the pathological alterations, the authors noticed that the chief features were in the hair follicles and sebaceous glands: "cystic dilatation, destruction of the hair, atrophy of the epithelium and a heavy plug of keratinized material which partly filled the cystic cavity." Besides the cutaneous lesions, the patient complained of general symptoms similar to those previously described: "lassitude, loss of appetite and loss of libido." The general symptoms actually did not focus the attention of the authors who considered that "the complaint of lassitude was not borne out by anything more than the usual temperament of the Negro toward work".

The eruption occurred during the manufacture of chlorinated biphenyl from benzene that contained excessive quantities of toluene, xylene and paraffin as impurities. As the patch tests with chlorinated biphenyl and the foreign substances, styrene dichloride and (2-chlorethyl)benzene, failed to provoke an acneiform eruption except in one case, Jones and Alden hypothesized that heating and chlorination of the impurities resulted in the production of styrene dichloride and (2-chloroethyl)benzene which, on contact with the skin, could be responsible for the acneiform eruption by the liberation of hydrochloric acid. They thought it was improbable that the cutaneous disease was influenced by the quantity of chlorine present but was more likely due to the formation of unstable chlorinated hydrocarbons as well as the the workers being in close contact with these causative agents without, subsequently,thoroughly cleaning their skin. The authors also discounted internal absorption as being responsible for the symptoms and regarded the possibility of of tar itself being responsible as improbable. Finally, they refused to name the eruption "chloracne" or "tar acne" and suggested labelling the disease "acneiform dermatergosis" as White had previously done (Jones and Alden, 1936).

In 1937, Butler observed 21 workers who were handling a mixture of *o*-(2-chlorophenyl)phenol sodium and [2,3,4,6-]-tetrachlorphenol sodium and were afflicted with an "enormous number of comedones and numerous sebaceous cysts. In some cases, comedones were so numerous as to

produce a black discoloration. […] The eruption began with a few papules behind the ears; then it spread to the forehead, cheeks, chin and back of the neck.[…] Two patients who had previously had acne of the face showed, in addition, involvement of the abdomen, penis, scrotum and the anterior surfaces of the thighs." Patch tests were positive with *o*-[2 chlorophenyl] phenol sodium. The patients were removed from the plant in which they used to work; 15 months later they had not completely recovered (Butler, 1937).

Seven cases of chloracne were reported by Meigs et al. among 14 workers exposed to Aroclor® from 5 to 19 months, intermittently. Six of them had a normal liver function test. One had borderline results. As the lesions were exclusively on the exposed areas, the authors inferred that the vapours were directly deposited on the skin (Meigs *et al.*, 1954). Chloracne was also observed on 15 employees who had painted sections of glass with enamel that actually contained Aroclor® (Birmingham, 1942).

Finally, wrote Schwartz et al., chloronaphthalenes and chlorobiphenyls are so acnegenic that every worker sufficiently exposed to these substances for a few months will develop acne-like lesions on the exposed parts of their body. Thus,"the manufacture of the chlorinated hydrocarbons and the coating of wires and condensers with insulating materials containing the chlorinated hydrocarbons should be done in totally enclosed processes so that the fumes of the insulating substances and of the solvents, if any are used, do not come into contact with the workers" (Schwartz, 1936; Schwartz *et al.*, 1947).

In 1954, Kanegafuchi Chemical Industry started PCB production in Japan; occurrences of chloracne were reported from that time. Hara [Japan], in 1969, reported a 20% to 30% incidence of cutaneous symptoms among workers who had been employed in a capacitor factory between 1953 and 1963. In 1972, ?Hasegawa? [Japan] reported an acneiform eruption and brown chromodermatosis of the dorsal joints of hands, fingers and nail beds and comedones on the face, thighs and backs of employees working in similar activities (Cordle *et al.*, 1978).

In 1979, Fischbein et al. conducted a clinical survey of 326 capacitor manufacturing workers [168 males and 158 females] in order to evaluate the health effects associated with occupational exposure to PCBs. Dielectric fluids containing PCBs [i.e. Aroclor®] and chlorinated benzenes had been used for 30 years. Each worker was questioned on their past and present occupational history and their past medical history. The duration of PCB exposure varied from less than 5 years to more than 25 years. Of the studied population, 40% had been employed for 20 years and 45% of the male workers and 55% of the female workers had a history of dermatologic complaints. A skin rash was reported in 39% of workers; a burning sensation in 25%; a history of acne after beginning work at the plant in 11%. On physical examination, the authors noted a marked prevalence of abnormal dermatologic findings: 41% of the male and 38% of the female workers mentioned swelling, dryness and thickening of the skin and 5% had an acneiform dermatosis. As for extracutaneous symptoms, 18% had gastrointestinal symptoms and 40% of the male and 58% of the female workers had a history of neurologic symptoms (Fischbein *et al.*, 1979).

Ouw et al. reported a burning sensation of the face and hands, nausea and a persistent odour among 34 workers exposed to Aroclor® 1242 (a mixture of varying amounts of mono- through heptachlorinated biphenyls with an average chlorine content of 42%) in a capacitor manufacturing plant in Australia. One of them had chloracne without systemic effects and five exhibited an eczematous rash on the legs and hands. Although the authors failed to find a significant correlation between the severity of dermatitis and blood PCB levels, they noted that the cutaneous signs occurred more often among workers with high blood PCB levels (Ouw *et al.*, 1976).

In 1981, Maroni et al. investigated 40 male et 40 female workers exposed to Pyralene 3010 or to Apirolio, [mixture PCB containing 42% chlorine], in capacitor manufacturing. Fifteen of them exhibited skin diseases, four had chloracne, four had folliculitis, one oil dermatitis, one acne vulgaris and five dermatitis secondary to irritation. Hepatomegaly and an increase in serum hepatic enzymes levels [γGT, ALAT, ASAT] were shown in 16 workers. No correlation was found between chloracne and serum PCB levels. According to the authors, the existence of percutaneous absorption risk was underscored by the detection of considerable amounts on PCB on the palms and soles of the workers. The authors, therefore, considered percutaneous absorption as the main route for systemic exposure (Maroni *et al.*, 1981).

A retrospective study was conducted on 2,567 workers who were employed for at least three months in areas where PCB was used. Mortality from all causes including cancer was lower than expected. However, increased mortality for cancer of the rectum, the liver and the breast was noted. However, none of these results was statistically significant (Reggiani and Bruppacher, 1985). As previously shown, in families of workers exposed to chlorinated derivatives, raised serum PCB levels were reported in wives who laundered their husbands' work clothes (Fischbein and Wolff, 1987).

Epilogue

Although chloronaphthalenes were progressively replaced by silicones and plastics in the 1950s, chloracne caused by chloronaphthalene was still observed, mainly because of the low cost of these materials. In 1958, Hubler [Corpus Christi, Texas] reported eight cases of chloracne in patients exposed to Unichrome chlorinated wax, used in chrome electroplating (Hubler, 1958). Quinones published two cases that occurred in patients working in a factory producing chloronaphthalenes (Quinones, 1950-1951). Newhouse presented the case of a male patient, employed in an engineering firm as a copper platter, who was exposed to Halowax® (polychloronaphthalenes) (Newhouse, 1967). Kleinfeld's publication in 1972, on 92 workers exposed to a mixture of tetra- and pentachloronaphthalenes, seems to be the last on this matter. The first cases of dermatitis appeared after four months exposure to the materials. It was observed that the ventilation failed to draw the air sufficiently quickly to ensure proper evacuation of the fumes emitted by the hot chlorinated wax. Then 59 workers exhibited skin lesions; 56 of those could be linked to chloronaphthalenes exposure. The face and arms were the most affected areas. In addition,

the female workers complained of general symptoms that might indicate systemic toxicity: headaches, asthenia, vertigo and loss of appetite. The tests of liver function performed on five workers who had the most severe cutaneous lesions did not show any biological alteration. However, as no test was performed on the other employees, the authors could not assert the absence of hepatic alteration caused by chloronaphthalenes (Kleinfeld *et al.*, 1972).

In 1974, Taylor still listed about 100 industrial applications of chloronaphthalenes (Taylor, 1974). Four years later, the Centers for Disease Control [CDC] published occupational health guidelines for hexachloronaphthalenes that mentioned that the acne-like eruptions and the liver toxicity of Halowax® might lead to yellow liver atrophy and death ([Anonymous], 1978d). The last US producer of polychlorinated naphthalenes [PCN] stopped manufacture in 1980.

According to the World Health Organization [WHO],, the major sources of chlorinated naphthalenes released into the environment are likely to be waste incineration and the disposal of items containing chlorinated naphthalenes to landfills (Stringer and Johnston, 2001). Chlorinated naphthalenes have also been shown to be highly bioaccumulative in fish. The amount of bioaccumulation observed increases with the degree of chlorination of the chlorinated naphthalenes, but the most highly chlorinated naphthalenes [e.g., octachloronaphthalene] do not appear to bioaccumulate due to their very limited absorption. Chlorinated naphthalenes can be absorbed via oral, inhalative and dermal routes, with absorption and distribution over the whole body after ingestion. Liver and fat tissue [besides kidney and lung] are the main target organs. Chlorinated naphthalenes, especially dioxin-like congeners, have also been detected in blood and breast milk samples from the general population ([Anonymous], 2001).

The concerns about PCBs increased when Jensen discovered its ubiquitous presence in the environment: “In 1964, the department of analytical chemistry at the University of Stockholm […] was required […] to estimate the levels of chlorinated pesticides, especially 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane [DDT] and its metabolites that were present in human fat tissues. […] Dried homogenates of muscle samples were considered to be suitable for the experiments. […] The final fat-free extracts were injected into a gas chromatograph. […] Only DDE (dichlorodiphenyl-dichloroethylene) and DDT could be identified by means of their retention times. Among these two, there were numerous peaks whose retention times did not agree with any of the known chlorinated pesticides. They were totally unknown to us. […] Fortunately for this investigation, a white-tailed eagle was found dead in the Stockholm archipelago. It contained enormous amounts of the unknown substances. […] It took about two years to answer the question of the mysterious peaks of the unknown substances in the chromatogram. Thus PCB was finally identified in 1966. […]” (Jensen, 1972b).

Then Jensen noted that PCB levels were higher in fish-eating sea eagles than in fish collected from the same areas. He inferred that the unknown molecule could persist in living tissue. In 1969, he showed that PCBs were present in high concentrations in marine animals of the Baltic Sea (Jensen *et al.*, 1969). PCBs had thus entered and accumulated along the food chain. In the same

period, it appeared that the three seal species in the Baltic Sea were in decline. High levels of DDT and PCB were detected in these species. It became then possible to correlate the infertility of female seals and elevated concentrations of PCBs.

Koppe and Keys underlined the fact that the toxicity of PCBs change during bioaccumulation through the food chain which tends to concentrate congeners of higher chlorine content. Bioaccumulated PCBs appeared, therefore, to be more toxic than the commercial ones due to the concentration of the most toxic forms. The May 1972 Task Force on PCBs identified three sources: environmental contamination [fish from lakes and streams]; industrial accidents involving leakage and spillage; and PCB fluids coming into contact with animal feeds, food or food packaging materials [PCB migration to food packed] (Cordle *et al.*, 1978).

The first international decision, taken in 1973 by the Organisation for Economic Co-operation and Development [OECD], required that the use of (new open products?) be banned. In 1976, the Toxic Substance Control Act required that "PCB could be manufactured, processed, distributed only in a totally enclosed manner" ([Anonymous], 1980b). Production of PCBs ended in 1978 in the UK and in 1979 in the US ([Anonymous], 1976), whereas in Eastern Europe, production continued until the mid-1980s. PCBs were banned in 2004 by the Stockholm Convention on Persistent Organic Pollutants [POP] (Hagen and Walls, 2004).

Today, exposure to PCBs may occur in various situations: using old television sets and refrigerators made 30 or more years ago that may leak small amounts of PCBs into the air when they get hot during operation; breathing air near hazardous waste sites and drinking contaminated well water; during repair and maintenance of PCB transformers; and accidents, fires or spills involving fluorescent lights ([Anonymous], 2014a; [Anonymous]). In fact, 90% of human exposure is via contaminated food, mainly fish [especially sportfish caught in contaminated lakes or rivers], meat, and dairy products (Reggiani and Bruppacher, 1985).

From Nitro to Seveso

The accident that happened at a Monsanto plant in 1949 opened a new period in the history of accidental exposure to chlorinated derivatives that reached a climax in 1976 with an accident in Seveso which resulted in high exposure of the local population, including children, to TCDD, with deleterious consequences. These events highlighted the relationship between herbicides and chloracne as one of the main aspects of the history of chloracne. TCP and its derivative 2,4,5-T were at the centre of the concerns, all the more because they were widely used as insecticides, fungicides, herbicides, antiseptics, mold inhibitors, dyes and pigments, therefore often in contact with humans, either during their manufacture or during their domestic uses (Mergel, 2011).

Monsanto plant, Nitro, West Virginia

In 1922, Rubber Service Laboratories purchased a plant in Nitro (West Virginia) as war surplus and began production of chemicals and additives for the growing rubber industry. Monsanto Company - founded in 1901 by John Francis Queeny, who named his society after his wife, Olga Mendez Monsanto – subsequently purchased the plant in 1929. Production of trichlorophenol began in the fall of 1948. In this process, 1,2,4,5-tetrachlorobenzene [TCB], sodium hydroxide and ethanol were all added to the autoclave. Heat was applied and, when the pressure reached the desired point, the autoclave was vented.

On March 8, 1949, a violent reaction occurred when the temperature and pressure within the autoclave in Building 41 became excessive. The relief valve opened and the fumes and tarry residues from the contents of the autoclave were discharged into the atmosphere and into the interior of the building (Zack and Suskind, 1980). One hundred and twenty-two workers affected by the accidental exposure were documented in a company report a few months after the event (Ashe and Suskind, 1949-1950; Suskind, 1953; Thornton, 1990).

First cases

One of the first men to return to Building 41 after the explosion was "a 32-year-old steam fitter, Ivan McClanahan [who] experienced a burning sensation of the eyes, nose and throat. […] Skin symptoms occurred six days after the accident. His face became inflamed and there was a marked swelling over the eyelids, nose and lips. A few days later pustules, comedones and cysts began to appear on his face, forearms, shoulders, neck and trunk. […] McClanahan's skin became pigmented and he complained of being easily fatigued and feeling weak. […] One month after the exposure [he] experienced aches in his thighs and calves. […] he was virtually immobilized for a number of weeks. […] Thirty-six-year old Paul Willard, the chief operator in Building 41, had similar

symptoms.[…] In early July 1949, he was hospitalised; he was unable to walk. […] Two other patients Jesse Steele and 56-year-old Jonathan Hurley, examined at the same time, had almost identical problems. Chloracne was common to all four. So too was an odour; according to two doctors who examined them, when they were in a closed room together there was a strange odour similar to that of phenolic compound" (Hay, 1982b). Not only the workmen were affected but also medical personnel and even the Director of Safety, who was visiting the plant. Several wives of workers, who never came into the plant, were also affected with chloracne, as were a man who purchased a truck parked in the vicinity of the accident at the time it occurred and his child (Holmstedt, 1980). Between March and October 1949, 77 employees had cutaneous and other symptoms, probably as a result of the accident.

In April 1950, two additional employees had similar symptoms. In October, the men were "markedly improved". A "special treatment" was recommended for one of them because of emotional problems related to the skin pigmentation, which was so severe that "he had been mistaken for a Negro and forced to conform with the racial segregation customs of the area…. on buses and in theatres" (Thornton, 1990).

From 1949 to 1953, ten workers severely affected with chloracne were examined on three occasions. Acne persisted in a few cases, although greatly improved, whereas some of the general symptoms - mainly pains, nervousness and fatigue - remained unchanged. Twenty-six additional workers had chloracne resulting from regular occupational exposure to 2,4,5-T. Among these 36 workers, 27 of them complained of pain, fatigue, nervousness, loss of libido and persistent skin lesions. Despite these symptoms, according to Suskind, the physician in charge of the early clinical examination, "there were no health effects that would impair a man's ability to work and [there was] no objective evidence of impairment of the liver, the pancreas or heart" (Thornton, 1990). These adverse effects were not published in the early 1950s but only in 1979, i.e. 30 years after the event. Then, from 1979 to 1994, epidemiologists and Monsanto's physicians reported on the long-term effects of the 1949 accident and regular exposure to chlorophenols.

Epidemiology studies

In June 1979, Suskind [Kettering laboratory] carried out a clinical study on 436 employees of the plant to identify the possible long-term effects of trichlorophenol. The population included the workers exposed to the 1949 accident and the employees exposed to the normal process of manufacturing from 1948 to 1969. The control cohort consisted of persons who were never exposed to the 2,4,5-T process. Finally, the cohorts consisted of 204 exposed persons, 163 not exposed and 51 of questionable exposure.

Suskind found that 86% of the exposed employees had developed chloracne from 1949 to 1969; on examination in 1979, 52.7% still had chloracne. Among the exposed workers, 14% did not develop chloracne. No employee belonging to the non-exposed group had chloracne.

Associations between the persistence of chloracne and the presence of elastic tissue degeneration of the skin and between exposure and gastrointestinal tract ulcers were found. Suskind failed to find any evidence of increased risk for cardiovascular disease, hepatic disease, renal disease, central or peripheral nerve problems or reproductive problems among the exposed workers and among those who had chloracne. Only a very limited number of cases of chloracne had occurred in 2,4,5-T users and among people living in a contaminated environment and no systemic effect was documented. Suskind concluded that the frequency and severity of chloracne were related to the degree and extent of exposure, that the highest frequency and severity of the disease occurred mainly in production workers and that the systemic signs either clinical or biological always followed the onset of chloracne. He inferred from these observations that chloracne is the hallmark of TCDD absorption and biological response a hallmark of intoxication (Suskind, 1985).

In 1980, Zack, a Monsanto epidemiologist, and Suskind, published a standardized mortality analysis on workers exposed in the 1949 accident. Only the workers who had developed chloracne resulting from the initial accident were selected. Of these, 32 had died at the time of the study: 9 from malignant neoplasms [5 from lung cancer, 4 of those being cigarette smokers], 17 from circulatory diseases, one from a disease of the respiratory system, 3 from external causes and 2 from other diseases. The total was actually less than the 46 expected deaths. The authors concluded that the study did not indicate any apparent excess of total mortality due to malignant neoplasms or circulatory diseases (Zack and Suskind, 1980).

In 1983, Zack and Gaffey, both employed by Monsanto, examined the mortality of Nitro plant employees who worked some time between January 1, 1955 and December 31, 1977, with at least one year of occupational exposure to 2,4,5-T. They identified 884 white male employees. Within the cohort, 163 deaths were noted: nine from urinary bladder cancer, attributed to the use of 4-aminobiphenyl. *p*-Aminobiphenyl [PAB], used from 1941 through 1952 as a rubber antioxidant and dye intermediate, which was actually shown in 1954 to induce bladder cancer in dogs. In 1955, the carcinogenicity of PAB to man was confirmed; bladder tumours occurred among workers exposed to this chemical at two Monsanto plants. The minimum duration of exposure reported to have produced a bladder tumour was 133 days with a latent period ranging from 15 to 35 years. The Standardized Mortality Ratio [SMR] for bladder cancer was the only statistically significant SMR among those for malignant neoplasms.

Among the 163 deceased employees, 58 had been assigned to 2,4,5-T production. Nine cancers were observed, six of which were lung cancers. Although not statistically significant, the SMR for lung cancer appears to be elevated. For the total Nitro plant study population, there was a statistically significant increase in deaths from arteriosclerotic heart disease (Zack and Gaffey, 1983).

After the death of the above mentioned workers, a class action was filed by seven retired employees. On May 1, 1985, “a Federal jury found […] that the Monsanto Company was not responsible for the illness of [these] employees who said they had been poisoned on the job by

dioxin. The jury did allow the damage claim of one of the seven whose illness was linked to another chemical. The seven men had contended that their lingering medical problems, including skin cancer, bladder cancer and a variety of nervous disorders, stemmed from exposure to dioxin and five other chemicals at the company's plant at Nitro, where they had worked an average of 35 years. They had sued the company for $4 million each in compensatory and punitive damages. The jury awarded $200,000 to one of the plaintiffs, John Hein, who was diagnosed as having bladder cancer in the course of the ten-month trial in the Federal District Court. The jury concluded, after five days of deliberations, that Mr. Hein's illness was linked to his exposure to PAB, a rubber additive produced from 1951 to 1953 at the Nitro plant" ([Anonymous], 1985).

In 1984, Suskind and Hertzberg authored an additional publication on the long-term health effects of exposure to 2,4,5–T. Two cohorts of Nitro plant workers were studied: 204 workers involved in 2,4,5-T production from 1948 to 1969 and 163 subjects employed at the same plant but never exposed to 2,4,5-T production or maintenance of the production facility. The authors admitted, however, they could not match the exposed and not exposed groups demographically; they also admitted that since 2,4,5-T was used ubiquitously as a weed killer in gardens, the possibility of additional exposure for both groups existed. Taking this into account, they noted that 52.7% of the workers exposed still had chloracne at the time of the study. By contrast, none of the workers who had not been exposed experienced chloracne. The authors found a statistically significant increase in the history of upper-gastrointestinal tract problems between those exposed and those not exposed; they failed to find any difference with regards to birth defects. With regard to cancers, they did not observe "an excess of cancer of all sites […] in the mortality analysis of the group exposed […] Cancer of the liver was not observed in this study population nor was an excess of cirrhosis noted" (Suskind and Hertzberg, 1984).

The same year, Moses et al. published their results on 226 current or former workers employed at Nitro between 1948 and 1977. They found a history of chloracne in 52% of them. The mean duration for residual chloracne was 26 years. A higher mean of gamma glutamyl transpeptidase, a significant higher prevalence of abnormal sensory findings and an increased prevalence of reported sexual dysfunction and decreased libido were reported among workers with chloracne compared to those not affected by this condition. Although mean triglyceride values were higher in those with chloracne, the difference was not statistically significant. No difference was found between those with and without chloracne in serum cholesterol, total urinary porphyrins or in reproductive outcome (Moses *et al.*, 1984).

In 1993, Collins et al. published the last study, on 754 employees who had been working at the Nitro plant between March 8, 1949 [date of the explosion] and November 22, 1949 [date of the last reported case of chloracne resulting from the accident clean-up]. The cohort was divided into four groups : 461 workers without chloracne and not exposed to PAB; 171 workers without chloracne but exposed to PAB; 97 workers with chloracne, without exposure to PAB; and 25 workers with chloracne and exposure to PAB. The authors reported three deaths from soft-tissue sarcoma [STS],

one in the group without chloracne but with exposure to PAB and two in the group with chloracne and exposure to PAB. An increase in urinary bladder cancers occurred in all groups, but mainly in the group without chloracne exposure but with exposure to PAB (Collins *et al.*, 1993).

Published by Monsanto's physicians or sponsored by the Company, the reports can be summarized in a few points: chloracne occurred in more than half of the exposed workers; the mean duration of chloracne was 26 years; the analysis of mortality failed to indicate any increase in death from circulatory diseases and cancer, except for the bladder cancers caused by PAB; differences in smoking habits could explain the elevated SMR for lung cancers and arteriosclerosis; the serum levels of gamma glutamyl transpeptidase in workers with chloracne was significantly raised; and significant abnormal sensory findings, sexual dysfunction and decreased libido werefound in workers exposed to chloracne.

These relatively reassuring reports were the object of much criticism. Some pointed to methodological flaws regarded as preconceived views aimed at denying Monsanto's responsibility. Others stressed that the results were published in the post-Vietnam war period when Monsanto and other manufacturers were accused by Vietnam veterans of being responsible for chemical-related diseases [see further on Agent Orange].

Controversies surrounding Monsanto's reports and their reliability

Hay pointed out how different the results of the Monsanto surveys were compared to those published by BASF in Germany, Philips-Duphar in The Netherlands and Spolana in Czechoslovakia [see later] that showed higher incidence of gastrointestinal cancers, heart attacks and bronchogenic cancers (Hay, 1980b). Moreover, when comparing Zack and Suskind's publication with Zack and Gaffey's, Hay and Silbergeld observed that four workers were listed as exposed to TCP in one paper whereas the same workers were listed as not exposed in the other. They also remarked that in the second paper, 19 workers who died of cancer or circulatory diseases may not have been included in the exposed group whereas they fitted the criteria for inclusion.

Hay and Silbergeld pointed out that one of the problems with Monsanto's reports was the determination of exposure in the Nitro plant: the patients exposed during the 1949 accident were considered as being seriously exposed as they had developed more severe chloracne than the workers occupationally exposed for several decades. According to these authors, to classify the levels of exposure on the only basis of chloracne that would reflect high-dose exposure might be inappropriate as lower and/or chronic doses might also cause cancers. Hay and Silbergeld proposed that the data provided by Monsanto be reassessed and suggested that the total cohort of workers should be considered "as a whole without making a distinction between workers exposed to dioxin in the TCP process accident or when making 2,4,5-T " (Hay, 1985).

Beside the criticisms issued in scientific papers, other analyses questioned the reliability of Monsanto's reports and the responsibility of the company (Robin, 2009). Thornton [Greenpeace]

accused Monsanto of being responsible for a "manipulation of data and study methods in order to obtain the predetermined result that dioxin had no negative effects on worker health" and for minimizing the heath effects of dioxin on Vietnam veterans. Greenpeace's report also labelled as "improper" the "use of chloracne as the sole marker of dioxin exposure in one study. […] the dilution of the chloracne study group with cases of dermatitis and other skin diseases unrelated to dioxin exposure; the use of variably and contradictory study criteria." Finally, concluded Thornton, "the data and manipulations of the three Monsanto studies render them essentially meaningless" (Thornton, 1990).

Cate Jenkins, a chemist at the US Environmental Protection Agency [EPA], acting as a whistle-blower, stated that if the studies by Zack and Suskind [1980] and Zack and Gaffey [1983] had been conducted correctly, they would have shown the connection between dioxin and cancer in humans. Jenkins also underscored the methodological problems and denounced "numerous other flaws in the Monsanto health studies. Each of these misrepresentations and falsifications always served to negate any conclusions of adverse health effects from dioxins." Because of the false information provided by Monsanto "dioxin has been given a lesser carcinogenic potential ranking which continues to be the basis of less stringent regulations and lesser degrees of environmental controls." Moreover, wrote Jenkins, the Monsanto studies published in the 1980s "have been a key basis for denying compensation to Vietnam veterans exposed to Agent Orange and their children suffering birth defects from such parental exposures" (Jenkins, 1990). In a letter to Fingerhut (National Institute for Occupational Safety and Health [NIOSH]), Collins, a Monsanto epidemiology director, rejected "the accusation of fraud in these two epidemiology studies [that] have been raised by a person untrained in and unfamiliar with the science and methods of epidemiology. […] the two Monsanto studies called into question have been published in literature for ten years […] If there are serious scientific problems in either of these studies, these issues should have been raised in a scientific forum. […] No challenge in a scientific forum has ever appeared. […] the accusations of fraud in these two studies are untrue. While there have been some changes in our perception of who had potential for significant exposure in the Zack and Gaffey study, these changes, reported by us, were incorporated to give us a better understanding of the potential for risk from exposure to dioxin. These changes did not alter our original study conclusions. We firmly stand behind the published conclusions of these two studies" (Collins, 1990).

Sanjour,from the EPA, also pointed out that these studies coincided with a time when Monsanto was defending itself in three different legal actions against veterans of the Vietnam war exposed to Agent Orange who attempted to obtain compensation from the Veterans Administration [VA] and from the manufacturers of Agent Orange [Monsanto, Dow Chemical notably] (Sanjour, 1994).

In 1990, after the previous studies sponsored by Monsanto had been denounced as fraudulous, the EPA launched a criminal investigation that was closed in 1992, without coming to a definite conclusion on the reliability of the studies (Roberts, 1991b). In 2004, 5,000 residents in Nitro filed a

class action lawsuit for over 50 years of exposure to dioxin. In February 2012, Monsanto settled the lawsuit, agreeing to pay $93 million for medical testing and environmental clean-up (White, 2012).

Nordrhein-Westfalen

The plant at Nordrhein-Westfalen was engaged in the production of pentachlorophenol [PCP] - extensively used as an insecticide and fungicide to impregnate wood, leather, paper, paints and glues - from August 1948 until February 1949. The attention of Baader et al. was drawn to the hazard involved in the plant by the compensation claims of 10 to 17 workers employed in the PCP production department.

The first signs of chloracne were reported by the foreman of the plant in December 1948, i.e. five months after the beginning of PCP production. Ten workers in all were affected by an acne - "disseminata punctata with varying degrees of secondary pustular infection, small and large furuncles, brown pigmentation and some cicatrisation." A year later, four workers still had severe acne and four others showed various signs of the disease. In one case, the lesions were slight; the acne of only one worker had completely disappeared. Eight of ten men examined had a history of neuralgic pain of the lower extremities occurring during their skin disease. Four workers still complained of bronchitis. Other disorders were registered, including heart complaints [palpitation] and loss of libido [four cases]. Results from laboratory analyses were within normal ranges. The authors pointed to the similarity between their observations and those made by Teleky [Pernakrankheit] in which skin disease was associated with neuralgic symptoms [see above] (Baader and Bauer, 1951).

Badische Anilin und Soda Fabrik AG [BASF], Ludwigshafen

BASF was founded on April 6, 1865, in Mannheim, in the county of Baden, by Friedrich Engelhorn. On November 17, 1953, the autoclave used for the alkaline hydrolyse of TCB into TCP in the BASF plant in Ludwigshafen, exploded. This was followed by the release of steam through a broken security valve; an intense vaporous haze quickly filled the autoclave room. After several minutes, the clouds had precipitated in the form of a white layer, covering appliances, walls, window panes, doors and other surfaces so that the room was declared sufficiently clear to be entered.

Seventy-five workers were exposed. Within a few days - from two days to two weeks - 55 of them were afflicted with chloracne. Of this number, 21 had only skin disease, 14 had chloracne and involvement of various organs [4 hepatitis, 1 had kidney disease, 5 had bronchitis, 1 had fatal pancreatic necrosis, 3 had various diseases including myocarditis] and 7 had chloracne and alterations of the central nervous system (including encephalitis) or of the peripheral nervous system (Goldmann, 1973). Wheeler [Monsanto] reported that "the photographs of the worst Badische cases show horrible skin eruptions with nearly blister-like welts and some ulcerations

where infection ensued. Areas involved included the face, neck, arms and the upper half of the body. […] In addition to the skin manifestations, the men reported all the additional symptoms as experienced in our workers, i.e. fatigue, vertigo, loss of libido, painful joints etc" (Wheeler, 1956).

About ten days after the accident and after clean-up, Oettel [MD, BASF] exposed rabbits to the workroom atmosphere and observed the effects provoked by the chemicals released. Nothing happened until one week after the exposure when the animals died. Necropsies revealed liver necrosis. Oettel first hypothesized a virus infection and exposed additional animals, both in the operating room and in cages suspended inside the decontaminated autoclave as well as in the adjacent department. All died within one to two weeks after exposure. BASF investigated the TCP process and isolated so-called "impurities". According to Oettel these impurities could show up in the production of any chlorinated phenols and might be responsible for chloracne. Oettel and Irish [Dow Chemical] suggested that the most potent chloracnegen was a compound similar to a polychlorinated diphenyl oxide [i.e. 2,2',4,4',6,6'-hexachlorodiphenyl ether] with hydroxyl substituents, such as 4,4'-dihydroxy-2,2',5,5'-tetrachlorodiphenyl ether for instance.

After they had failed to reproduce chloracne on the rabbit-ear test using 2,4,5-T, Wheeler and Weger [Monsanto], Oettel [BASF] and Suskind [Kettering Laboratory] decided to employ human volunteers in an attempt to evaluate the acnegenic potential of various process materials. Halowax 1014 [a known acnegen] was chosen as a control (, compared to?) 2,4,5-T. Both materials were applied to the forearms of the human volunteers. Liver function tests were conducted every other day. In two to three days, redness developed in the Halowax exposure and in ten days there were some follicular changes. No systemic change appeared.

Although the investigators did not observe any systemic change after experimenting with Halowax on humans, Oetell considered chloracne "also may be systemic in its origin." He stated that Halowax and TCP were not acnegenic in themselves and declared his conviction "tetrachlorobiphenyl dioxide" (i.e. TCDD)was responsible. It was later pointed out that the significance of this information reported during the June 12, 1956 meeting, i.e. a year before Kimmig and Schulz's report [see further], might have been overlooked because the participants did not refer explicitly to "dioxin" but to its archaic name "chlorinated biphenylene dioxide" or "chlorinated biphenyl oxide". These names were actually replaced by "dioxin" after 1957 (Huff and Wassom, 1973). Oetell also indicated that BASF no longer produced TCP but purchased it from Bayer and used a bromosulphtalein retention test to evaluate the liver function in rabbits and to accept or reject each TCP lot (Suskind and Oetell, 1956).

Five years after the explosion, a worker who had entered the contaminated area became ill and died The circumstances were reported by Thiess et al.: " the man aged 57 years was welding one of the autoclaves and therefore wore all the protective clothing as well as a welding mask. While heating a bearing of an autoclave stirrer, he lifted the mask several times to wipe sweat from his forehead. The heat developed by the welding flame had caused the lubricant of the bearing to vaporize and he apparently inhaled these fumes. Four days later, acute dermatological and

neurological symptoms developed. Six months later, the man was hospitalized because of enlargement of his liver and pancreas. After nine months, a large mass of tissue appeared in the left upper abdomen, with symptoms of an acute inflammatory process resulting in renewed hospitalization during which the patient died. An autopsy revealed pancreatic necrosis, perforation of the stomach and the duodenal bulb, liver abscesses and chloracne on the trunk. No measurements of the concentrations of dioxin were taken at the time of the accident because the substance was still unidentified in 1953" (Thiess *et al.*, 1982).

In 1978 – i.e. 25 years after the initial event - 17 workers had died : 6 from cancer, 5 from cardiovascular disease, 1 from cirrhosis of the liver, 1 from urogenital disease and all others from accidents or suicide (Huff *et al.*, 1980). No abortion was reported among the wives of exposed employees still at work. As a consequence of these findings, an epidemiological study was initiated in 1982 to evaluate the mortality rate of the exposed workers, including those who assisted in demolishing the autoclave in 1968 and 1969 and those employed to clean up the building after the explosion. Seventy-four workers were successfully traced. It was concluded that "the mortality rate for natural causes of dioxin-exposed employees was as expected for the Ludwigshafen population, the administrative district of Rhinehessia-Palatinate and the Federal Republic of Germany. Although based on comparatively few deaths, malignant neoplasms were found to be consistently above expectations. The effect, however, was shown beyond chance only for stomach cancer". A reanalysis of the BASF cohort presented in 1989 revealed a statistically significant increase in cancers of the respiratory and digestive tracts (Rohleder, 1989).

Forty years after the accident, Zober et al. set up a retrospective study the aim of which was to describe the long-term morbidity rate of exposed workers and to determine whether they experienced higher cause-specific morbidity than comparable non-exposed employees. The study group consisted of 158 men. It was divided into three subgroups based on chloracne state: subgroup I consisted of 52 workers whose chloracne was extensive or severe; subgroup II consisted of 61 workers with moderate chloracne or erythema at the time of the exposure; subgroup III consisted of 45 men without chloracne or erythema. Overall illness rates were positively correlated with the prior chloracne state. The authors observed increases in infectious diseases, respiratory diseases, mental disorders and diseases of the peripheral nervous system. Unspecified neoplasms were not significantly increased in the severe chloracne and high TCDD subgroup. Chronic liver diseases were marginally increased in the high TCDD subgroup (Zober *et al.*, 1994). Contrasting with these reassuring data, Thornton [Greenpeace] quoted a presentation made by Rohleder at the 1989 international symposium on dioxin, who asserted that reports had been manipulated by BASF to disguise an elevated rate of digestive cancers (Thornton, 1990).

Boehringer, Hamburg : evidence of 2,3,7,8 tetrachlorodibenzo-*p*-dioxin's responsibility

In 1954 and 1955, 24 employees working at the Boehringer plant, Hamburg who had been employed in the production of, or had handled, TCP since 1953 and the first months of 1954 were affected with chloracne on the face, nape of the neck and arms. They also complained of general symptoms: loss of appetite, headache, nausea, fatigue, loss of libido and, in two cases, alterations of heart rhythm. In 1976, chloracne was still visible in 11 of the 24 workers. Few of them still complained of the general symptoms initially observed. Neurological disorders were present among several workers who were so greatly affected that they were receiving compensation. Two workers from the original group had died (Hay, 1982a).

A defining event in the history of chloracne occurred in the summer and autumn of 1956, when Kimmig and Schulz observed an outbreak of chloracne in workers manufacturing TCP. Of the 31 workers afflicted, 9 had severe symptoms, 14 an intermediate form of chloracne and 8 had light symptoms. Erythema and oedema of the face preceded acne lesions, mainly comedones on the face, earlobes and neck. In the most severe cases, the lesions extended to the chest, back and arms. The majority of the patients complained of blepharo-conjunctivitis, asthenia, weight loss, and loss of appetite. The authors failed to find any biological disturbances of liver and kidneys. As for pathological alterations, Kimmig and Schulz confirmed the previous findings: epidermal acanthosis and enlargement of the pilosebaceous follicle, which was filled with corneous material.

In cooperation with a chemist named Georg Sorge, Schulz obtained samples of 2,4,5-T. The sample with the highest purity did not elicit a skin reaction when applied to a rabbit ear – a method invented by Adams several years earlier for testing the cutaneous effects of chemicals (Adams *et al.*, 1941) – while the samples ["commercial grade"] for use in the production processes of 2,4,5-T production did. Schulz and Sorge inferred that some impurity might be responsible for the chloracne. At the same time, in 1957, Sandermann [Hamburg university] was synthesizing TCDD while investigating new chlorophenols for use as wood preservatives. Some of the dried compounds blew accidentally onto the face of one of Sandermann's assistants. As he developed chloracne, he was referred to Schulz who suspected a possible relationship between the compound and the skin disease. Sorge recognized that dioxin could be the causative agent. Then he isolated TCDD from the commercial grade sample of TCP and compared it with dioxin he had prepared. Both compounds were identical and caused a positive response during the rabbit-ear test. Schulz did not hesitate to test the TCDD solution on his own forearm, which provoked a localized chloracneiform response. Schulz and Sorge had finally found the cause of the chloracne that occurred among the Boehringer workers (Kimmig and Schulz, 1957; Schulz, 1957).

Following this discovery, the industrial process in the Hamburg plant was modified - Sorge developed a low-temperature procedure for production in a closed system - so that the incidence of adverse effects was lowered before the company finally decided to dismantle the plant (Firestone, 1978). Boehringer also informed other chemical companies manufacturing TCP how they could

avoid the by-product of TCDD (1957; Boehringer Sohn, 1957; Smith, 1957). However, Boehringer's experience did not lead to containment of the dangers associated with the chemical process (Holmstedt, 1980). In 1961, i.e. few years after Schultz's discovery, more than 100 workers exposed to chlorophenol derivatives in three different plants in Hamburg and the vicinity still exhibited chloracne associated with skin pigmentation, blepharo-conjunctivitis, various general symptoms [fatigue, loss of appetite], gastritis, dyspnoea, hepatic symptoms and various neurologic and psychiatric symptoms, notably [headache, paraesthesia, hyperaesthesia, depression] (Bauer *et al.*, 1961). Finally the plant was closed on June 18, 1984.

Philips-Duphar, Amsterdam

In the explosion that occurred in Amsterdam in 1963, about 100 workers - between 90 and 140 according to the reports - were exposed to 2,4,5-T. Between 30g and 200g of dioxin were released in the factory hall. A morbidity cohort of 141 men exposed and accessible to follow-up, was constituted and divided into 69 workers who had chloracne and 72 with equivocal cutaneous symptoms. In 1983, 25 men had died, 8 from neoplasms and 8 from myocardial infarction. Among them, 7 had had chloracne; 4 of them were employed by the contract cleaners and did the dirtiest job. They had been exposed to various chemicals before and after the accident and their alcohol consumption was relatively high. Their deaths from malignant tumours were not considered to represent an excess mortality. The TCP plant was closed in 1973 (Dalderup and Zellenrath, 1983). It was then dismantled brick by brick. The rubble, embedded in concrete, was dumped into the Atlantic.

Diamond Alkali, New Jersey

In 1964, Bleiberg published the first occurrence of chloracne and porphyria cutanea tarda in 11 of 29 workers employed in the Diamond Alkali plant, New Jersey, manufacturing dichloro and trichlorophenols. A few biologic and pathologic alterations of the liver were noted: increased transaminases, and cell regeneration of the liver. Skin biopsies from the post auricular area showed the pathological hallmark of chloracne: disappearance of sebaceous glands. The authors suspected an intermediary substance - chlorinated phenolic acid containing six chlorine atoms - as the possible causative agent due to its extreme volatility. Ultimately, the relationship between chloracne and porphyria cutanea tarda remained unclear (Bleiberg and Brodkin, 1964; Bleiberg *et al.*, 1964; Mount, 1964).

Seven years later, Poland studied 73 male workers employed at the same plant; none of them had clinical signs of porphyria cutanea tarda but 13 of them [18%] experienced chloracne. The workers who were most exposed to various chemicals had the most severe forms of chloracne. Sixteen workers had facial hypertrichosis and 30 had hyperpigmentation, significantly correlated with the severity of acne. Whereas 11 workers had uroporphyrinuria and 3 had porphyria cutanea

tarda in the study conducted by Bleiberg six years before, Poland et al. did not find any porphyria cutanea tarda (Poland *et al.*, 1971).

Dow Chemical, Michigan

The production of PCP at the Dow Chemical plant [Midland, Michigan] started in 1939; TCP production started in March 1950.

In early 1964, 49 out of 61 workers complained of a skin disease diagnosed as chloracne. The severity ranged from questionable to severe. Among the workers employed prior to July 1964, chloracne was observed in 30 of 34 people in the high-potential-exposure group and 14 of 16 in the low-potential-exposure group. Following this episode a meeting took place at Dow Chemical headquarters on March 24, 1965, gathering together representatives from four rival companies: Biochemical Research Laboratory [Dow Chemical], Wilkenfeld and Verhoeze [Hooker Chemical Corporation], Kennedy , Chandler [Diamond Alkali Company] and Dunn and Frawley [Hercules Powder Company]. A representative of the Monsanto Chemical Company was invited but did not attend.

Holder MD, reviewing the Dow experience reported that about 60 to 70 cases of chloracne had been identified. He described an "acute chloracne" that appeared within five to eight days in some individuals after a pronounced single exposure. A liver biopsy was performed on a man affected with a rather severe form of chloracne which did not show any pathological alteration. With regard to general symptoms, fatigue was the only significant sign. Holder mentioned that for some workers the duration of the skin disease could be as long as two and a half years. After a discussion on the TCDD analysis and the mandatory precautions regarding the handling of dioxin samples, there was an agreement that the participants could not afford to sell contaminated products (Silverstein, 1965). The March 1965 meeting was made public almost 20 years later. *The New York Times* suspected that at this time "Dow was extremely frightened that this situation might explode" (Burnham, 1983).

Experiments on prisoners

Rowe, consultant to the vice-president of Dow Chemical Company, then Director of Toxicological Affairs, pointed out that one of the basic problem was "to learn to correlate the response observed in humans with that observed in rabbit ears. […] We also need to know something about the basic changes that occur in the skin in response to given acnegens. What is the effect of the microflora of the skin and what, if any, treatment can be instituted to alleviate the condition once it begins to develop? (Rowe, 1964)". In this respect, on December 24, 1964, Rowe informed the Company's board that he had contacted Kligman, renown Professor of Dermatology at the University of Pennsylvania, to compare the effects produced by TCDD in rabbit ears to the effects produced in humans. Kligman who tested the chloracnegenic potential of TCDD on prisoners was paid $10,000 for his services (Reiter, 2009).

Kligman's research in the penal system had actually started in the early 1950s when an outbreak of athlete's foot occurred at Holmesburg Prison [Philadelphia]. "Dr Kligman identified 1951 as the year he received a call from Holmesburg Prison, shortly after he had discovered the PAS stain for visualizing fungi. When Dr Kligman entered the aging prison he was awed by the potential it held for his research : "all I saw before me were acres of skin. It was like a farmer seeing a fertile field for the first time" (Hornblum, 1998).

In fact, in the early 1950s, Kligman published two papers that drew attention to his research on fungal infections, including human experimentation,, as he wrote in the *Journal of Investigative Dermatology*: "the data reported in this paper derived from observations on experimentally infected humans. The work was carried out at a state institution for congenital mental defectives where tinea capitis was endemic and the inmates subject to constant opportunity for infection. The experimental circumstances were ideal in that a large number of individuals living under confined circumstances could be inoculated at will and the course of the disease minutely studied from its very onset. Biopsy material was freely available." Commenting on the article, Weidman, Emeritus Professor of Research in Dermatology and Mycology at the University of Pennsylvania, emphasized Kligman's work: "the employment of human test subjects is ideal […] we secured splendid cooperation on the part of the inmates. They are anxious for any kind of attention" (Kligman, 1952). Hornblum suggested that after Weidman's judgement - that ignored the Nuremberg Code enunciated a few years before - Kligman became persuaded that the use of an institutional population was perfectly acceptable.

Rowe informed Kligman about the experiments already carried out on animals and on the precautions needed for human testing with dioxin: " I am sending to you under separate cover a small amount of 2,3,7,8 tetrachlorodibenzo-*p*-dioxin. This is the material which is a potent acnegen and is highly toxic. […] We find that when the total dose does not exceed about 2.2 of a microgram of the acnegen, no follicular prominence or epithelial hyperplasia develop […] and 4 to 8 micrograms always produce a severe response. We have not as yet been able to quantify the dose required to cause 50% mortality from skin exposure. […] In view of this information, it does not seem probable that the dosages shown in the accompanying suggested protocol for the human work would be likely to constitute any serious systemic hazard. […] Nevertheless, the seriousness of the consequences that might develop from testing with this type of compound requires that we approach the matter in a highly conservative manner.[…] The observations are to be made at your discretion but I would urge routine SGOTs and alkaline phosphatases as a minimum" (Rowe, 1965).

This human experiment on dioxin started in late 1965 and was completed in 1966. Hornblum reported Rowe's testimony before the EPA on this matter that described Kligman's procedure: "Dr Kligman reported that the subjects were divided into six separate groups of ten each. The first group was studied in two phases: initially, a single dose of 0.2 microgram was administered; after a two-week interval, the same total dose was administered to the same skin site in two daily doses of 0.1 microgram. […] The application site was covered for 24 hours by a 2-inch gauze square. One week

after the single dose and three to four days after the final daily dose, chemical tests were performed on each subjects […] haematology test […] kidney function tests, […] liver function tests. A the end of each phase, the subjects were examined by an internist for signs of systemic illness. The skin was examined weekly for six weeks after the last dose. […] There was not the slightest bit of acne, either on the forehead or the back […] no subject developed symptoms that could be related to the treatment." [quoted by Hornblum, p 168].

In 1968, i.e. one and a half years after the beginning of the experiments Kligman reported that "not a single subject developed acne nor was there any evidence of toxicity. This encouraged me to proceed more vigorously. We then assembled a new panel of ten subjects and applied 0.5 ml of a 1% solution in alcohol chloroform to a one-inch square on the back. These applications were made every other day for one month. The treated sites were covered with a non-occlusive gauze square. Each week for six weeks, the following laboratory tests were carried out: urine analysis, CBC, BUN, SGOT, alkaline phosphatases and creatinine clearance. Clearly the exposure was immensely greater than the former one. Eight of ten subjects showed acneiform lesions usually beginning after three to four weeks. This began like a typical development of comedones. In three instances, the lesions progressed to inflammatory pustules and papules. The lesions lasted four to seven months since no effort was made to speed healing by active treatment. […] The histologic and clinical manifestations were in every way compatible to classical chloracne. […] In no instance was there laboratory or clinical evidence of toxicity. The subjects remained well throughout the study. […] It is a certainty that the rabbit ear is exceptionally sensitive to acnegenic chemicals and is an excellent system for the detection of such chemicals. Finally, it may be said that chloracne closely mimics acne vulgaris. The only difference is the paucity of anaerobic organisms in the comedones. One may conclude that bacteria are not very significant in the pathogenesis of chloracne" (Kligman, 1968). The total dosage given to the ten prisoners was 7,500 micrograms. In the end Kligman failed to find the definition of a threshold exposure for the induction of chloracne by TCDD in man. [quoted by Hornblum p 169].

Rowe pointed out that the protocol he gave Kligman was "conservative…. and very specific, but I had no control if he decided to change it". Rowe added that Dow toxicologists "were startled when they realized that Kligman had altered the protocol by increasing the dosage 468 times. His protocol was quite amazing and it caused us to sever the relationship" ([Anonymous], 1980c).

The experiments conducted by Kligman were first publicized on January 11, 1981 in the *Philadelphia Inquirer* in an article entitled *"Human guinea pigs : dioxin tested at Holmesburg"*. Then other newspapers including the *New York Times* summarized Kligman's experiments : "somewhere, almost certainly in the United States, are as many as 70 men who could help researchers determine the risks of human exposure to the poison called dioxin. The 70, whose identities have been sought without success by investigators for the EPA, are the only people known to have been deliberately exposed to measured external doses of dioxin. All were subjects of tests commissioned by the Dow Chemical Company and conducted in the 1960s on the skin of inmates

who volunteered at Holmesburg Prison in Northeast Philadelphia. […] No records of the prisoners' identities appear to have been kept and there were no follow-up studies after the testing period. Some experts suspect that complications can occur many years after exposure to dioxin. The tests were conducted for Dow by Dr. Albert M. Kligman, a dermatologist at the University of Pennsylvania. Ten of the subjects were treated with dosages far exceeding guidelines set by Dow. The company wanted to determine the "threshold," or minimum amount, that could be expected to produce chloracne."

In a report this year on the inability of the EPA to identify the men in the experiment, Frank L. Davido, a pesticides investigator for the EPA, wrote, "The agency believed that records relating to Dr. Kligman's studies could have provided additional information on the risks associated with the uses of 2,4,5-T and Silvex (2-(2,4,5-trichlorophenoxy)propionic acid, editors note) because the precise dermal dosages of TCDD in the studies were apparently known." […] Dr. Kligman has declined to be interviewed, or to discuss his experiments at any length. But, in a brief telephone conversation, he said: "All those people could have leukaemia now - about one chance in 20 billion. And I could be hit by an asteroid when I walk out on the street, but I don't think I will." He said he had given all his test records to Dow. "I believe that included the names," he said. A Dow spokesman, Robert Charlton, said the company had never had the names. Health officials for the City of Philadelphia and Holmesburg, as well as Dow and Dr. Kligman, have told the environment agency they have no records to help identify the men.

Dr. Kligman's tests for Dow Chemical were discovered by the EPA in hearings the agency conducted in 1980 on whether the two Silvex and 2,4,5-T herbicides, which are restricted to some agricultural uses, should be prohibited altogether. Hearing records provide ample documentation of the tests and how they were conducted, but offer no clues to the identities of the subjects except to show that most were black and ranged from 21 to 49 years of age. They were paid for participating in the experiments. […] Also, according to documents filed at the 1980 hearing, an earlier experiment by another Philadelphia doctor had tested solutions ranging from 2.5 % to 10 % of Silvex, which tends to contain a dioxin contaminant, on the skin of 51 volunteers, believed also to have been prisoners. At 5 %, the solution caused "primary skin irritation," according to a Dow summary of a report by Dr. Joseph V. Klauder, a dermatologist then also associated with the university. (No Records or Names Found.?) Dr. Klauder died about ten years ago. Neither his test records nor the names of his subjects are available. […] On May 11, 1966, ten months after he apparently received the material from Dow, Dr. Kligman reported "astonishingly negative results" to the company. He had used six groups of ten men, though a few dropped out during the test period. The dosages had not exceeded 16 micrograms and the men had been given liver and kidney tests. "No subject developed symptoms that could be related to the treatment," he said in a later report. Mr. Rowe authorized more experiments and Dr. Kligman conducted a second set of tests. "In January of 1968," Mr. Rowe said in testimony at the 1980 hearing on use of the pesticides, "I was surprised to receive a letter from Dr. Kligman reporting new results." Dr. Kligman's message was

that, with a "new panel of ten subjects," he had increased the total application to about 7,500 micrograms. […] Dr. Kligman did not testify at the EPA hearings, but Mr. Rowe did. “Did you or Dow consider whether the human subjects you had exposed to TCDD had developed cancers in the years subsequent to the conduct of the study?" Andrew Gordon, an agency attorney, asked. "We have not followed up on that," Mr. Rowe said. He was also asked whether he would call Dr. Kligman's application of 7,500 micrograms the conservative approach Mr. Rowe had requested. "No sir, I wouldn't," he responded. When the dioxin tests were first disclosed, by *The Philadelphia Inquirer* in 1981, 40 prisoners and former prisoners got in touch with the EPA, believing they had been among those tested. Nine of the men were interviewed, but Mr. Davido concluded that it was hopeless to try to determine which of them might have been subjects of the dioxin tests” (Robbins, 1983).

Ackerman, a leading dermatopathologist who worked with Kligman at Holmesburg in 1966, reported complementary details on the circumstances of the experiments: “About a week after I arrived, the FDA banned Kligman from doing research because he had fabricated data in studies of DMSO at Holmesburg. Moreover, the FDA had forbidden him from doing that research and he had gone ahead with it anyway. He disappeared from Penn until mid-September, so I never made it to Holmesburg Prison until then. I did research at Holmesburg for about nine months and then, for reasons various, left Penn to go to Harvard. […] The prisoners were being paid; it was little, but they were being paid; we were giving them a distraction from the miserable routine of prison life; and many of the prisoners not only served as “volunteers”, but many of them actually ran the experiments, so we were preparing them for jobs in laboratories or in other medical institutions after they left prison. […] In the early 1950s, he realized that doing experiments on prisoners was a vehicle for making lots of money. Even though he was not a very good businessman in the sense that he oversaw the details of the operation carefully - he left that to others - he understood very well how to seduce the pharmaceutical companies, and they were pleased to be seduced. […] Kligman came to Holmesburg only on Saturday mornings and not every Saturday morning, because he travelled a lot. He was a very popular speaker; he was all over the world. In a 52-week period, Kligman was probably at Holmesburg Prison 30 times.[…] In the late Fall of 1966, I invited my younger brother, who then was Chairman of Orthodontics at the Dental School at Penn, to visit Holmesburg. I wanted him to see what was going on there; I was proud of it. One look around and he said, “Have you ever heard of the Nuremberg Code?” That started me thinking. Up to that point, I’d never heard of it. Nobody at Penn, certainly not Kligman, ever mentioned it” (Goldfarb, 2006).

Additional chloracne cases

From 1950 to 1971, Ott et al. [Medical Department, Dow Chemical] conducted a study on 204 workers exposed to 2,4,5-T during its production in the Dow Chemical plant. The authors underlined that many of the workers had been exposed to numerous other chemicals as the unit was responsible for manufacturing various substances. Medical records of the employees were reviewed.

No case of chloracne or porphyria cutanea tarda was found. The mortality of the group was regarded as comparable to that of US white males. Only one death was reported due to a respiratory malignancy discovered in a retiree smoking two packs of cigarettes per day (Ott *et al.*, 1980).

As of December 1978, four deaths - one due to cardiovascular disease and three due to malignancies - were observed among the workers exposed to TCP in 1964, compared with the seven to eight expected. The authors admitted however that due to the small size of the cohort the results were of low statistical power (Cook *et al.*, 1980). A year later, the review of medical records revealed four cases of soft tissue sarcoma (STS). Two of them were cigarette smokers and had chloracne. Cook suggested that smokers who exhibited chloracne as a consequence of TCDD exposure might be at increased risk of STS (Cook, 1981).

Bond et al. [Dow chemical company], reviewing medical charts for almost 2,200 chemical workers potentially exposed to chlorinated dioxins from 1937 to 1982, concluded that 16% of them had been affected with chloracne. They also noted the incidence of the disease was highest among the youngest workers and among those who had been working in the production of chlorinated phenols rather than with products derived from those materials (Bond *et al.*, 1989). A year later, the authors compared their coding of chloracne with the coding of the same records done by the investigators of the NIOSH. As a result of the recoding, 246 workers were considered as having chloracne instead of the 346 initially indicated. However, despite the reclassification the mortality from all causes combined and from all neoplasms remained low. One case of STS persisted. The slight increase in mortality from cerebro-vascular disease noted in the first classification disappeared due to the fact that two of the four original chloracne cases were reclassified to no chloracne (Bond *et al.*, 1990).

Rhône-Poulenc, Pont-de-Claix, France

In 1956, in Pont-de-Claix [Isère, France], Colomb observed 17 patients exposed to TCP after an explosion at a Rhône-Poulenc factory; all of them were affected with typical chloracne, extensively and minutely described. The disease was characterized by the absence of erythema preceding the onset of comedones. No pruritus was mentioned by the patients. The neck and chest, flanks, abdomen, genitalia and thighs were affected by numerous comedones some of them being quite large. The most typical aspect was observed on the earlobes sometimes deformed by monstrous sebaceous cysts. Colomb described a greyish-yellow coloration of the face of a few of the patients. On the rest of the tegument, the number of comedones could give the appearance of a pigmentation, more or less generalized (Colomb, 1956). Dugois and Colomb confirmed the grey-brown colour that gave the face a “dirty and creased aspect”. Patients also complained of asthenia, loss of appetite, headaches and weight loss. The French authors also underlined a strange symptom they regarded as a mark of chloracne: even after ceasing his activity on the production of chlorinated compounds for several months, the patient still released an odour of chlorine.

The dermatosis was marked by remissions and exacerbations, sometimes quite harmful. Dugois and Colomb hypothesized these periods were the consequence of foreign body reactions due to the pruritus caused by the sebaceous cysts. They also pointed out that healing was not regularly obtained. The French authors then accepted Schultz's hypothesis that the responsibility lay with the dioxin formed during chlorophenol synthesis (Dugois and Colomb, 1957; Dugois *et al.*, 1958).

A similar event occurred ten years later on October 4, 1966. Within two days after the accident, 22 workers in contact with the product exhibited erythematous lesions, pruritus and oedema on the face. It was said that about 100 men were actually affected. A few days later, the lesions had disappeared; they were followed within two weeks by a typical chloracne consisting of comedones, some of them inflamed, on the face [forehead, temples, cheeks], neck, shoulders and forearms. Some patients complained of pain in the hepatic area. The inflamed lesions faded whereas the corneous ones remained, sometimes a year after the accident. The authors hypothesized that the toxic product – (4,4'-dihydroxy-2,2',5,5'-tetrachlorodiphenyl?) ether, formed during the production of TCP - was inhaled then slowly eliminated and was responsible for the cutaneous lesions (Dugois *et al.*, 1968).

Spolana plant, Czechoslovakia

In 1965, two technicians from a plant in Spolana developed chloracne during the evaluation of a new production process of 2,4,5-T, probably because of careless work and defective equipment. In 1968 and 1969, 55 workers from the same plant were admitted to the Department of Occupational Diseases of the University Hospital in Prague. Chloracne was observed in 95% of them, associated with feelings of sickness, weakness in the lower extremities and frequent pain under the right costal arch. Of the 55 workers, 20% exhibited cutaneous signs of porphyria cutanea tarda. Half of the patients had metabolic disturbances [elevated lipids and pathological changes in the glucose tolerance test]. A third had biochemical alterations that indicated the existence of mild liver lesions [steatosis, periportal fibrosis]. Two patients died from bronchogenic carcinomas, one from bronchopneumonia, two from traffic accidents and one from macronodular cirrhosis. Except for these workers, all patients have improved but none of them was completely healthy after ten years. All of the 18 children born to intoxicated individuals were free of developmental abnormalities. The wives of two patients had spontaneous abortions in their third month (Jirasek *et al.*, 1976; Pazderova-Vejlupkova *et al.*, 1981).

Coalite and Chemical Products Ltd, Bolsover

The production of TCP at the Fine Chemicals Unit of Coalite and Chemical Products Ltd, Bolsover, Derbyshire began in August 1965. "At midnight on 23 April 1968, […] ethylene glycol and orthodichlorobenzene vapours were released in quantity in the atmosphere. In the presence of atmospheric oxygen these constituted an explosive mixture which appeared to have been detonated

by an overhead electric lamp" (May, 1973). After investigation, a white crystalline solid of high toxicity was isolated and proved to be TCDD produced during the manufacture of TCP (Milnes, 1971).

Due to the violence of the explosion, the supervising chemist, Eric Burrows, was killed by falling masonry. May, the company doctor, who also contracted chloracne through contact with affected workers, examined 14 employees present in the building at the time of the accident: 2 workers complained of tiredness, 3 of tightness of the chest and 11 had biological abnormalities, mainly hepatic. Ten days later all tests were normal. Then all men developed a cutaneous eruption which was diagnosed as chloracne. Hay also reported the case of Ernest Taylor, who exhibited chloracne two weeks after he began to work in the damaged plant. He regarded this period as "a very worrying time. You could eat and sleep but didn't dare go out in company because your face was in such a mess" (Hay, 1982a). From May 8 to December 8, 1968, 79 cases of chloracne were recorded. Within the next four to six months the majority of them had recovered. The outbreak of chloracne forced the company to close the plant and to introduce rigorous hygiene procedures.

Production of TCP resumed in 1969, in a new plant modified according to new safety procedures. Three weeks later, two workers employed there, the son of one of them and the wife of the other, showed a skin disease diagnosed as chloracne (Jensen, 1972a; Jensen *et al.*, 1972). The investigation revealed that the workers had been contaminated by a single piece of equipment and then passed the disease to their relatives by contact at home. In 1973, 7 cases of chloracne were still observed in workers in the new building. The total number of cases of chloracne came to 90. One death was recorded among the involved workers. As the rabbit ear tests produced the same results as those previously obtained in the Boehringer plant [see above] the responsibility of dioxin in the Coalite event became obvious.

After the Seveso accident [see later] that raised concerns about TCP, Coalite's management was incited to reassure the public through articles published in national papers on August 13, 1976: "the Coalite 2,4,5-trichlorphenol unit incorporates the most modern, automated, failsafe systems. As part of our normal annual holiday shut down arrangements the unit was already idle when the Seveso accident was first reported. Although it was ready to start up a week later, we appreciated that anxieties arise and decided it should remain shut down. We shall NOT [sic] make any decision on reopening it until we have satisfied not just ourselves but also our workforce, the local authority and the Government's Health and Safety Executive that is 110% safe."[quoted by Hay, The chemical scythe]. Despite this hopefully reassuring statement, the local press and local population remained concerned by the contamination of the site. Coalite's management finally declared on October 14, 1976 that the plant would close permanently.

A year later, on the demand of the Health and Safety Executive [HSE], it was decided to carry out a study of the state of health of the workers present at the time of the explosion. Three groups were constituted: group A: no dioxin exposure [31 employees]; group B: possible dioxin exposure [54 employees]; and group C: dioxin exposure with chloracne [41 employees]. In group C, about

50% of the workers still exhibited mild chloracne. The children of parents in all three groups were still alive and healthy. In group C, there were three miscarriages. Increased gamma glutamyl transferase and triglycerides were found in all groups.

Ten years after the accident, no deaths from neoplasms had been reported. May concluded that the monitoring of the workers who had chloracne in 1968 or later and who were still employed by the company showed no significant difference from their colleagues, either those exposed to dioxin without any cutaneous signs or those never in contact with dioxin. As for the skin lesions, the great majority of the workers had a complete recovery and even those who had chloracne quite severely in 1968 had recovered (May, 1983). May, however, insisted on the necessity of a wide analysis to draw definite conclusions with regard to the long-term health effects of dioxin exposure (May, 1982).

Besides the survey carried out by May, Coalite commissioned Blank, Ward [Sheffield University] and Martin [Chesterfield Royal Hospital] to perform additional series of tests. They failed to show any chromosome damage in the exposed workers, howeve reduced levels of IgD and IgM and raised levels of serum cholesterol and triglycerides were observed. After she had completed her study, Martin was informed that Coalite refused that the results be published. She was also informed that the control group was inhomogeneous, and therefore devalued the comparison between the exposed and non-exposed groups. Given these circumstances, Martin carried out a second study that confirmed the results obtained in the first one: increased serum cholesterol and reduced serum high density lipoprotein in a group of eight workers affected with chloracne, all factors that implied an increased risk for cardio-vascular disease. Martin admitted that the number of subjects was obviously too small to regard the results as statistically significant (Walker and Martin, 1979).

The HSE could not obtain the full medical reports from Coalite but only a version where no difference between exposed workers and a control group was mentioned. This problem was revealed to the scientific community on March 6, 1980 in *Nature*. According to Hay, Coalite had decided not to publish the true results on the advice of Crow, a consultant dermatologist at St Margaret's Hospital who was unsatisfied with the statistics used in the report. Crow strongly denied having advised Coalite not to publish the report (Hay, 1980a; Hay, 1981).

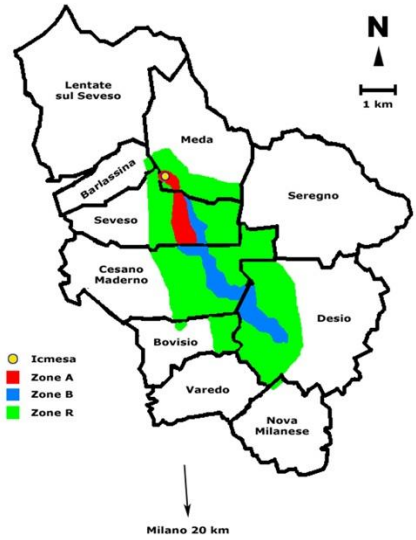
Seveso, Italy

On Saturday 10, July 1976, six and half hours after the plant had closed down for the week end, during a period of hot weather "a cloud came out of a chimney at the ICMESA factory owned by the Geneva-based company Givaudan [with about 170 workers] located in the town of Meda on the northern outskirts of Seveso", a small town with about 17,000 inhabitants between Lake Como and Milan. In this plant, built in 1970 and 1971, Industrie Chimice-Meda-Societa Arionaria [ICMESA] had produced compounds for the cosmetic and pharmaceutical industries, including TCP, since

1975. On Saturday July 10, 1976, "excessive pressure induced by an exothermic reaction in the TCP vessel occurred some hours after suspending operations and caused the disk of the safety valve to break down. […] TCDD burst through the roof and spread directly into the atmosphere. […] a 5 m/s wind was blowing and the emission cloud contaminated the ground along a linear path from about 6 km, south-eastward from ICMESA. Unfortunately, this cloud covered inhabited areas" (Mocarelli, 2001). Whereas previous accidents involving dioxin exposure had remained confined to the production plant and the workers, in Seveso, the reaction led to the discharge of TCDD over an area of 2.8 km^2 that affected a large population, including children and adolescents (Homberger *et al.*, 1979).

The local police was informed of the explosion the day it occurred. Seveso's mayor and Givaudan's management were informed of the accident on Sunday. July 11. Two days after the event, the health authorities reassured the population and declared that "there was no fear of any danger to the people living in the area surrounding the plant" (Pesatori and Bertazzi, 2012). The first deaths of animals were reported on Wednesday, July 14 (or 15 according to different sources). On the following day, the Mayor of Seveso and Meda declared an area south of the ICMESA factory to be polluted and banned the consumption of local fruits and vegetables.

Samples were collected from the reactor for analysis. The laboratory checked the TCP produced to be sure that the dioxin levels were acceptably low. The results were obtained on July 15. They confirmed the presence of dioxin in quantities of parts per thousand. The first medical reports made on July 16 were reassuring regarding the health of the ICMESA workers. The first reports of children suffering from skin rashes were made on July 16. Nineteen infants were hospitalized (Hay, 1982a).



On Saturday, July 17, the ICMESA factory was pronounced polluted and orders were given for the destruction of all vegetables, fruits and animals in the contaminated area. Closure of the ICMESA plant occurred on July 18. The contaminated area was divided into three zones according to the concentration of TCDD in the soil; additional criteria included the presence of dead animals: zone A (110 ha, 736 inhabitants) was the most contaminated area, with TCDD concentrations in the soil higher than 50 $\mu g/m^2$ (up to 580 $\mu g/m^2$); zone B (270 ha, 4,737 inhabitants) was a long narrow strip located south of zone A, containing

Figure 12. Map of Seveso with the different contaminated zones. A. Highly polluted (5-50 µg/m2 TCDD). B. Less polluted (<5 µg/m2 TCDD). R. Control zone. 5-50$\mu g/m^2$ TCDD, and considered polluted, but people could stay in this zone; an area of 1,430 ha (31,800 inhabitants) surrounding zone B was coded zone R - R for respect - where TCDD concentrations in the soil were less than 5 $\mu g/m^2$. A fourth zone, S, was actually added outside the contaminated area and was used as a control zone (Fortunati, 1985) (Figure 12).

TCDD was identified only two weeks after the explosion and confirmed by Givaudan on July 26. The monthly production of TCP was about 5 tons. The reaction initiation at the origin of the explosion was completely unexpected, and subjected to various theories, including sabotage. In 1981, Theofanis Thefanous, a chemical engineering specialist, in collaboration with Givaudan, found a scientific explanation for the accident, involving an exothermic reaction starting below the previously known threshold of 230°C (Theofanous, 1981).

The disagreement over the quantity of TCDD released in the explosion has been pointed out: 2.5 kg to 3 kg according to some authors, up to 130 kg of dioxin for others. According to Di Domenico et al., the amount should be estimated at 34 kg or higher (Di Domenico *et al.*, 1990). Soil analyses indicated that TCDD accounted for 90% of the total dioxins in the environment. In Zone A, the entire top soil layer [25 cm] was removed and replaced with fresh uncontaminated soil.

By July 22, although more than 30 people were suffering from burns, local authorities still insisted on the absence of danger and did not plan any evacuation. Such an attitude was all the more dubious given that several accidents involving TCDD in TCP plants had already occurred and the thermal decomposition of TCP to TCDD in alkaline solution was known (Milnes, 1971).

A program of evacuation was actually agreed on July 24 and began on July 27. Two hundred and twelve families [736 people] from Zone A were evacuated. People were advised not to eat fruit and vegetables from the area. Women in the first trimester of pregnancy were advised to move until the foetus was at least three months old. One hundred and fifty women who were in the first trimester of pregnancy at the time of the explosion applied for abortion despite the difficulties encountered by women who had decided to have an abortion in Italy a this time. In August, the Lombardy regional government ruled that pregnant women from the contaminated zones could have legal abortions. However, many local doctors refused to terminate pregnancies and only a small proportion of these women could get an abortion in Italy, many of them had actually to seek a termination abroad (Hay, 1977). Of the 34 foetuses? examined, only one had a malformation suggestive of Down syndrome. Most residents from Zone B and R were not moved; only children and pregnant women were evacuated. In this context, Pesatori and Bertazzi reported that “made in Seveso” so far used as a guarantee of high quality in goods, machinery and products became a stigma of contamination. Hotels refused to admit people coming from the Seveso area that was sometimes named “little Hiroshima”.

In July and August 1976, 1,660 people were examined: 447 of them exhibited dermatitis [erythema and oedema of exposed areas and vesiculo-bullous and necrotic lesions] affecting only persons directly exposed to the toxic cloud. During the two years that followed the accident, the medical commission in charge of the surveillance of 220,000 people in the contaminated area examined the health parameters considered to represent possible risks: skin lesions [chloracne], neurological lesions, liver and kidney function, blood abnormalities, growth of new-borns and children, birth defects, spontaneous abortions, cytogenic abnormalities, immunological deficiency, infectious diseases, birth rate and mortality rate.

Pocchiari et al. pointed out that epidemiologic data had not been processed adequately for several reasons: the nature of the accident made it very difficult to properly estimate the population at risk; the actual toxicity of TCDD was highly debated; various problems complicated the coordination of national, regional and municipal aid (Pocchiari *et al.*, 1979). Bertazzi et al. also underlined the hectic conditions that jeopardized the validity of many investigations no matter how carefully they were conducted (Bertazzi *et al.*, 1998).

Initial observations

Reggiani [clinical research director, Hoffman-La Roche Ltd] reported that "the first symptoms produced by the exposure were itching, redness and swelling of the skin which rapidly developed into lesions, resembling first and second degree burns with the formation of blisters and, later, crusts. Lacrimation and sensation of grit in the eyes were mentioned but conjunctivitis was not observed. […] The skin lesions, whose onset was noted three to seven days after the dispersion of chemicals were the complaint leading to hospitalization. […] The dermal lesions […] were of two types: 1. diffuse redness and swelling of the skin affecting mainly the exposed areas of the body. In some cases, vesicles, pustules and crusts were present and hyperkeratosis and vermicular atrophy occurred. […] acute initial pain which is typical of thermal burns was not mentioned. These skin lesions appeared between three and seven days after the accident and healed without recurrence after two to three months.[…] 2. eruption of blackheads, usually accompanied by cysts of different sizes but commonly not larger than a lentil. […] Their onset could be dated to between two weeks to two months after exposure. They started to appear when the other skin lesions were fading". Vesiculo-bullous and necrotic lesions present on the palms, buttocks and knees were attributed to contact with toxic substances had settled onto the soil. Papulonodular lesions were found on the trunk and upper limbs of a few children 15 days after the accident.

Chloracne began to appear in September 1976. From September to December 1976, 44 people had chloracne [27 females and 17 males, aged 2 to 20 years]. All were residents of zone A; 25 of them (Reggiani, 1980) exhibited comedone-like lesions symmetrically distributed on the malar areas and the ears. The nasal area was spared. Eleven patients had comedones and cysts on the face and nape of the neck. Eight patients had severe lesions that involved non-exposed areas. All these patients developed hyperkeratotic lesions on the limbs and three showed erythematous, granuloma annulare-like elements. No patient showed systemic involvement.

Gianotti, who had the opportunity to observe children a few days after they had been exposed to TCDD, reported corneous cysts on their faces and the dorsal aspects of their forearms. He also observed lesions looking like granuloma annulare on the dorsal aspects of the hands. In some children, a typical chloracne appeared a few weeks later. The less afflicted children exhibited only comedones on the cheeks. The pathological alterations were marked by an epidermal hyperplasia and mainly by the presence of corneous cysts in the sudoral ducts. Gianotti did not mention any alteration of the sebaceous glands (Gianotti, 1977).

Caramaschi et al. pointed out that it was not possible to determine the actual incidence of chloracne due to the fact that the information on the time of onset was reliable only in a limited number of cases. They found that thechildren with chloracne exhibited more elevated gamma-glutamyl transpeptidase and alanine amino-transferase than children without chloracne (Caramaschi *et al.*, 1981). Mocarelli et al. found similar results in children affected with chloracne in zone A (Mocarelli *et al.*, 1986).

In November and December 1976, six additional cases of chloracne were reported in adult patients living in Zone A. Serum samples from five Zone A residents who developed the most severe types of chloracne, four from Zone A who did not develop chloracne and five from Zone S were evaluated. The serum TCDD levels were the highest ever reported in humans, i.e. 56,000ppt (Mocarelli *et al.*, 1991). The three highest levels were from children with chloracne. It was thus concluded that these values could be used for correlating TCDD levels and adverse health effects ([Anonymous], 1988c).

Further epidemiology studies

In February 1977, among 32,200 children from the schools of Seveso, Meda, Cesano and Maderno, 85 cases of mild-to-serious chloracne and 153 cases which could not be classified were seen. Complementary investigations detected 52 additional cases. The majority of the patients was under 21 years old.

Three months later, 525 cases of chloracne were reported in a group of 25,000 children examined by dermatologists, many of them being outside the zone regarded as contaminated. After re-examination, on the order of the Lombardy authorities, fewer than 1 in 4 of the cases were confirmed. An additional screening was made in 1978. Six new cases of mild chloracne appeared and 95 cases could not be classified. It was concluded that even though all cases were classified as chloracne, the maximal percentage of chloracne cases in the four TCDD contaminated municipalities [Seveso, Meda, Cesano Maderno and Desio] would be 0.5% i.e. quite close to the 0.3% found in cities of Northern Italy not involved in the accident.

Most of the chloracne-affected patients were children aged 2 to 10 years or adolescents. The most severe chloracne occurred in subjects who had early lesions, the severity of the lesions being related to the length of TCDD exposure. In the two years that followed the accident, comedones and cysts progressively decreased in the majority of patients. A limited number of patients had biopsies that showed horny metaplasia with acrosyringeal cyst formation in the dermal and intraepidermal eccrine duct, dilated follicular ostia filled with cornified lamellae and foreign body granulomas around the detached walls of the excretory ducts of some eccrine glands.

From 1976 to 1982, 1,500 children from the three contaminated zones were studied. The mortality rate from all causes did not differ in any of the three contaminated areas from that of the control population. In Zone A, males had an increased mortality from cardiovascular disease and

females from chronic rheumatic heart disease. According to Bertazzi et al, the increased cardiovascular mortality rate might be related to the psychological stress due to the accident and to TCDD exposure. Lymphohaemopoietic neoplasms showed a statistically significant increase among males, whereas females had a six-fold elevated relative risk for Hodgkin's disease and myeloma. None of the 186 children who contracted chloracne died during a ten-year follow-up [1976-1986] (Bertazzi *et al.*, 1992).

The results of the first measurements of TCDD showed serum levels ranging from 828 to 56,000 ppt in ten children with chloracne. Nine adults without chloracne, from Zone A had TCDD serum levels ranging from 1,770 to 10,400 ppt. No significant differences in mean values of liver enzymes and lipids were detected in the chloracne group compared with a control group. No increased frequency of peripheral neuropathy was found. All patients underwent a yearly examination until 1985. Chloracne was the only abnormal finding. In July 1985, the lesions had completely disappeared in 110 patients, resulting in cicatricial lesions.

Finally, ten years after the accident, it was concluded that: chloracne is the most typical and reliable sign of poisoning by TCDD (Del Corno *et al.*, 1985); it appeared in a very small percentage of the most sensitive group of the population involved, children and adolescents; in the majority of cases, the skin lesions are mild or even extremely mild and healed rapidly; the acnegenic toxic action of TCDD lasts about two years; atrophic scars are the only sequel of the accident; no laboratory alterations of hepatotoxicity or porphyrin metabolism nor abnormal neurological findings were observed in cases with chloracne. No subject suffering from chloracne had developed systemic lesions or important laboratory alterations (Caputo *et al.*, 1988). Bertazzi et al. pointed out, however, that the results did not provide any conclusive evidence of long-term effects on the exposed subjects of the Seveso accident (Bertazzi *et al.*, 1998).

Investigations on long-term adverse health effects

Assennato et al. underlined the absence of effects other than chloracne and its complete reversibility 13 years after the event, which contrasted with previous data on TCDD effects observed in industrial accidents. According to the authors, several reasons might explain these discrepancies: in Seveso the inhabitants were exposed over a wide area, which led to a lower degree of exposure compared to those observed in industrial accidents, where workers were exposed to higher TCDD and TCP levels; the mild alcohol and drug intake in the affected population - i.e. mainly children - could explain the short duration of the biochemical abnormalities; the absence of abnormality ten years after the event could be explained by the decline of dioxin enzyme induction (Assennato *et al.*, 1989).

Twenty years after the event, Baccarelli et al. conducted a survey of 101 chloracne cases [56 males and 45 females] followed up since the accident and 211 controls [108 males and 103 females]. Among the control subjects, 101 of them were matched to chloracne cases by sex, age and

zone of residence at the time of the explosion. A questionnaire was administered by trained interviewers. Plasma TCDD was measured by the US Centers for Disease Control. TCDD plasma levels were still elevated in subjects who had eaten home-raised animals, in individuals who were older, with a higher body mass index and residence near the site of the accident. No cancer diagnosis was reported in chloracne cases. None of the children of the chloracne cases had birth defects, cancer, liver disease or diabetes. Chloracne was four times more frequent in subjects with current plasma TCDD > 10ppt. The authors underlined that even though several medical conditions had been reported in chloracne cases, frequency and types of disorders did not significantly differ between cases and controls during the 20-year life span that had been documented. They concluded that dioxin toxicity in these subjects was confined to the acute dermatotoxic effects. The authors also found a strong association between plasma TCDD levels and chloracne among subjects with light hair colour. As the explosion occurred in mid-summer, the authors hypothesized that UV exposure modified susceptibility to chloracne in fair-skinned subjects (Baccarelli *et al.*, 2005).

Finally after 20 years of observation, no significant health effects were mentioned, except chloracne, the only unequivocal effect found in the exposed population, although high levels of dioxins were reported (Needham *et al.*, 1997). After 25 years, only mortality from diabetes mellitus was found to have increased among females in all exposure zones, whereas the mortality from all cancers was not found to be elevated (Pesatori and Bertazzi, 2012).

Following the event in Seveso, the European Communities adopted, on June 24, 1982 a directive - now called the Seveso directive [directive 82/501/EEC] - “concerned with the prevention of major accidents which might result from certain industrial activities and with the limitation of their consequences for man and the environment” ([Anonymous], 1982). The 1982 Directive was amended into Directive 96/82/EEC and Directive 2012/18/EU that now apply to more than 10,000 industrial establishments in the European Union.

Additional chloracne cases among chlorophenol exposed workers

Stingily reported severe cases of chloracne due to exposure to sodium tetrachlorophenate used as a timber preservative (Stingily, 1940). The fine dust of chlorophenols,, when not carefully controlled, was also a chloracne producer, as reported by Butler, in men shovelling a fine powder of sodium tetrachlorophenate and *o*-phenol sodium into sacks in bad working conditions (Butler, 1937).

Regarding the accident in a Hooker TCP plant that occurred in 1956, few details are known. A similar event occurred in Thompson Hayward in 1959. The accident, denied by a company spokesman, was confirmed by workers. Dioxin exposure had also been reported at the Vedinger site of Bayer, West Germany in 1970 (Hay, 1982a).

In the early 1970s, 159 workers [157 men and 2 women] were exposed to TCDD during the production of TCP in a chemical plant in Linz, Austria. After the outbreak of chloracne had

occurred, technical improvements were introduced in May 1972 and the building closed in August 1973. Chloracne cases, however, occurred during the cleaning and reconstruction of the plant.

In 1991, Neuberger et al. examined nine male workers with a history of chloracne who had been exposed to TCP and 2,4-dichlorophenoxyacetic acid [2,4-D] production between 1971 and1973. They had experienced chloracne between 1972 and 1973. Seventeen years after the end of the exposure, the authors found a median concentration of 340 pg TCDD per gram blood lipid, i.e. 17 times the median concentration in the control subjects from the same plant who had not been exposed to the same chemicals. The authors, therefore, considered chloracne as a reliable indicator of heavy dioxin exposure (Neuberger *et al.*, 1991). In 1996, chloracne was still observed in 15 male and 1 female patients (Neuberger *et al.*, 1998). As for the children of exposed fathers, the difference in the number of girls and boys was supposed to be the result of more girls from fathers who were 20 years of age or younger when they were first exposed to dioxin (Moshammer and Neuberger, 2000).

In 1970, 128 workers in a USSR plant producing TCP for the manufacture of 2,4,5-T were reported with chloracne, headaches, fatigue, irritability, nausea, loss of memory and somnolence, a year after the production of TCP was begun (Telegina and Bikbulatova, 1970). A second examination was performed a year and a half later. Of the 128 workers, 13 had severe chloracne, 24 had moderate skin disease, 32 had minimal signs and 14 did not exhibit any cutaneous sign. A non-significant tendency of hypercholesterolemia was noted among the workers affected with the most severe form of chloracne.

Between 1969 and 1970, five of seven workers exposed to 2,4,5-T in a factory in Ufa, Russia exhibited chloracne. These workers still had elevated levels of TCDD [mean level: 185 ppt] 22 years later. The authors noted that two workers with higher TCDD levels did not exhibit chloracne. They pointed out, therefore, that while chloracne indicates dioxin exposure, its absence does not preclude such exposure (Schecter *et al.*, 1992).

In the early 1970s, 20 cases of chloracne occurred at a Monsanto plant in Newport, South Wales among workers exposed to PCP. The workers with chloracne had higher blood cholesterol and higher blood triglyceride levels than workers without chloracne. Those workers with chloracne were therefore regarded as being at greater risk of developing ischemic heart disease than any of the other groups. Hay reported that Monsanto considered these results were not reliable enough to be published in medical papers (Hay, 1982a).

In 1975, Oliver published the observations of three scientists preparing dioxin in government laboratories who experienced signs of intoxication. The first one - patient A - attempted to synthetize dioxin by heating TCP. Although he endeavoured to avoid skin contamination, eight weeks after he started the experiments, he began to exhibit a typical chloracne. He also mentioned headaches and fatigue. Two months later, his liver test functions were normal. Three years after the beginning of his experiments, the chloracne had almost completely cleared. The second scientist - patient B - who worked in a separate laboratory, noticed the appearance of a typical chloracne eight

weeks after beginning the experiments. Two years later he noticed general symptoms mainly marked by abdominal pain, loss of weight, headaches and irritability. He also noticed longer and darker hair growth on the shoulders and upper part of the back. All symptoms subsided over a period of six months. The last scientist - patient C - worked with patient B in the same laboratory. He never had chloracne but only a loss of energy that occurred three years after he started the experiments. Like his colleague, patient B, he noticed unusual hair growth on the shoulders and upper back. Oliver admitted that the relationship between the symptoms and the exposure to dioxin of patient C remained unclear. He also underlined the hypercholesterolemia noted in all three patients and concluded that the history of these patients emphasizes the high toxicity of dioxin even for laboratory scientists working with precautions. He also stressed that intoxication may occur without chloracne and that there can be a long period – two or three years - between the beginning of the exposure and the occurrence of the first symptoms (Oliver, 1975).

Sehgal and Ghorpade published the case of 20-year-old male worker who exhibited severe chloracne. Three months before the examination, the patient had been exposed to gas containing phenol. He experienced suffocation and dizziness. Similar episodes had occurred in workers exposed to fumes in the same conditions. The skin was covered with numerous comedones and pustules and abscesses on the face, chest and back, and on the proximal parts of the limbs. A skin biopsy revealed large sebaceous glands some of them filled with keratinous material (Sehgal and Ghorpade, 1983). The case, published by Cole et al., provided an additional illustration of the causative role of PCP in the occurrence of chloracne. About nine months after he had been treating lumber with PCP without the required protective clothes, a 32-year-old white male, who owned a firm which constructed piers for small boat marinas, noticed the onset of a skin eruption made of small yellowish-white papules over the whole body, but mainly located on the malar areas and retroauricular regions. The microscopic examination of the lesions, diagnosed as chloracne, revealed the absence of sebaceous glands without evidence of sebaceous metaplasia (Cole *et al.*, 1986).

Sweeney et al. compared 400 workers employed more than 15 years earlier in the production of TCP with an unexposed population. The prevalence of chronic bronchitis, peripheral neuropathy, depression, adverse cardiovascular effects, abnormal porphyrin levels and chronic obstructive pulmonary disease was not found significantly different from the control group. By contrast, statistically significant differences were noted in serum TCDD concentration and gamma glutamyl transferase, testosterone, triglycerides, abnormal HDL, fasting serum glucose and chloracne. Chloracne was associated with the highest serum TCDD levels (Sweeney *et al.*, 1997).

O'Malley et al. retrospectively studied the medical records of 648 workers involved in manufacturing PCP. They identified 47 cases of chloracne in workers assigned to PCP production in the same plant located in south-western Illinois between 1953 and 1978 (O'Malley *et al.*, 1990). It was said that the increase of chloracne cases observed by O'Malley et al was influenced by the initiation of a screening program in 1970 by the Monsanto Company (Leet and Collins, 1991).

Cheng et al. had the opportunity to examine 44 employees affected with chloracne. All of them were involved in the manufacture of PCP in a plant located 200km from Beijing. The workers said they had been affected by the disease for more than 15 years. The authors could find traces of TCDD in a sample of PCP (Cheng *et al.*, 1990). In 1994, Coenraads et al. examined additional workers in a Chinese factory producing PCP. Out of 118 workers, 34% were affected with typical chloracne, clinically and pathologically (Coenraads *et al.*, 1994). The same year, Jansing and Korff investigated eight workers involved in the manufacture of TCP or in the maintenance of a TCP plant between 1963 and 1976. All of them showed signs of chloracne. The blood TCDD levels measured were between 30 and more than 400 times the levels observed in the general population. Fifteen years after the exposure to TCDD had been discontinued, high blood levels of the chemical were still measured. The authors concluded that a correlation exists between the duration and expression of chloracne and the blood TCDD level (Jansing and Korff, 1994). Among 2,192 chlorophenol workers, Collins et al. examined 246 who developed chloracne after exposure to TCP or PCP. They had higher serum dioxin levels than workers without chloracne. The authors failed to find any evidence of increased death rates among the employees with chloracne. However, due to the limited number of deaths, they insisted on the necessity of complementary studies (Collins, 2007).

Miscellaneous chemicals associated with occupational chloracne

In 1955, a white operator employed in a chemical company in Houston, Texas was affected with a mild erythema of the face and forearms associated with an intense pruritus. He was employed in a trichlorobenzene unit used for one of the steps in the manufacture of DDT. A few days later, he exhibited folliculitis of the legs and an acneiform eruption consisting of comedones and papules that increased in severitywith indurated papulopustules. Four more patients with similar symptoms were observed. Although the clinical aspect was close to a chloracne, the authors did not find the disappearance of the sebaceous glands on microscopic examination of the lesions. The cutaneous symptoms persisted until the exposure of the workers to DDT production had been discontinued (Bowen and Moursund, 1957).

Deeken published the occurrence of chloracne in six workers involved in the manufacture of 2.6-dichlorobenzonitrile (dichlobenil) weed and grass killer [Casoron®]. The disease consisted of several hundred, pinpoint, open comedones and fewer closed comedones mainly located on the forehead, zygomatic and suborbital areas. The time between exposure and the first chloracne signs varied, ranging up to five months (Deeken, 1974).

In 1977, Taylor et al. described the first cases of chloracne caused by exposure to 3,3',4,4'-tetrachloroazoxybenzene [TCAOB], an intermediate compound formed during the manufacture of a new herbicide 2-[3,4-dichlorophenyl]-4-methyl-1,2,4-oxadiazolidine-3,5-dione [Methazole®].

Forty-one workers - 90% of employees - exhibited chloracne that appeared mostly in the first two months of their employment. Family members of four workers who had never been involved in the manufacture of TCAOB also experienced chloracne, probably due to contaminated clothes. The acneigenicity of TCAOB - that has chemical similarities with TCDD - was confirmed by the rabbit ear test (Taylor *et al.*, 1977).

In the late 1970s, an investigation was conducted among 102 employees in a pesticide and herbicide plant manufacturing Propanil® from 3,4-dichloroaniline [DCA] in Arkansas. The study revealed that 11% had been hospitalised, over a two-year period, for illnesses related to chemical exposure and 38% exhibited chloracne (Taylor, 1979). Scarisbrick and Martin also reported cases of patients affected with mild chloracne, working in two plants producing the herbicide Diuron® and its precursor DCA. 3,3',4,4'-tetrachloroazobenzene [TCAB] and TCAOB were identified as contaminants arising in the chemical reactions of the DCA process. Exposure to DCA/Diuron was associated with elevated blood triglycerides. No evidence of liver damage was found (Scarisbrick and Martin, 1981). McDonagh et al. reported 17 additional cases of workers professionally exposed to DCA who had comedones, some of them associated with xerosis, folliculitis, cysts and keratosis pilaris. Histopathologic examination showed that the sebaceous glands were sparse (McDonagh *et al.*, 1993). In 1985, Barrière et al. published the case of a 23-year-old man with a quite intense acne composed of comedones and pustules mainly located on the periorbital areas. The patient, a farmer, was exposed to the same herbicide as that involved in Taylor's publication. Although the skin biopsy failed to show the characteristic disappearance of the sebaceous glands, the authors retained "acné chlorique" as a diagnosis (Barrière *et al.*, 1985). In 1996, Vazquez et al. reported nine patients who had been working for several decades in a plant producing chemicals based on chlorobenzenes. All of them were affected with comedones and cysts predominantly on the malar areas, some of them on the nose, chest, shoulders, arms, buttocks and thighs. All patients reported conjunctivitis with a thick secretion from the meibomian glands. Seven patients had high levels of cholesterol and triglycerides. Although they did not mention the disappearance of sebaceous glands, the authors retained chloracne as the diagnosis (Rosas Vazquez *et al.*, 1996). Orris et al. observed two white male patients who had been fire-fighters for 20 and 23 years. One of them exhibited periorbital, pre-auricular, neck and axillary open comedones associated with pustules on the shoulders. The other had only periorbital comedones. Both of them had been exposed to silicon tetrachloride. The blood PCB levels were less than 10µg/l. Skin biopsies were performed; no mention was given of the appearance of the sebaceous glands. The authors regarded these observations as the first chloracne cases in fire-fighters (Orris *et al.*, 1986). An outbreak of chloracne was reported by Gawkrodger et al. among seven chemists aged 24 to 43, who synthesized a novel polycyclic halogenated chemical classified as triazoloquinoxaline, previously not known as a chloracnegen. Only one of the affected chemists had a low sebum excretion rate (Gawkrodger *et al.*, 2009).

Chloracne-associated food poisoning

According to Crow, the first occurrence of food exposure to chlorinated chemicals was noted in October 1945 when a fat-like substance found in the ruins of Berlin was used to fry vegetables (Crow, 1970). Three hours after eating fried potatoes cooked in the substance, a woman complained of headache and malaise. The following morning she noticed oedema of the face covered with numerous cutaneous lesions consisting of papules and yellowish nodules looking like sebaceous cysts. Her husband who had shared the meal exhibited a more severe form of the disease including a pleuritis. Four additional people affected in the same circumstances were examined in the Department of Dermatology of the Rudolph-Virchow Hospital [Berlin]. The diagnosis of chloracne was established (Hertzberg, 1947). Seven similar cases were examined at the Department of Dermatology in La Charité Hospital in Berlin. About 12 hours after the meal, all of them mentioned headaches and erythema of the face and neck. Then papules, nodules and sebaceous cysts giving the aspect of acne conglobata appeared on their forehead, nose, chest and back The fat-like substance used to cook was shown to contain a chloride derivative, probably chlorinated paraffin (Teller, 1947). Besides this unusual circumstance of human food poisoning, numerous reports were published on animals.

From 1941 till 1954, a mysterious (X-disease?) decimated cattle in Germany and in the US. The disease was actually due to the ingestion of highly chlorinated naphthalenes. In 1957, millions of chickens died in the eastern and mid-western parts of the US due to toxic components in feed fats. The disease was named chick oedema because it manifested with hydropericardium and ascites in chickens. Investigations showed that one of the factors responsible was 1,2,3,7,8,9 hexachlorodibenzo-*p*-dioxin.

In 1969, outbreaks of chick oedema occurred in North Carolina, resulting in the killing of more than one million chickens. The feed fat had been contaminated with TCP at a vegetable oil refinery in New Jersey. The inspection of a pesticide building located 100 yards from the vegetable oil refinery plant, revealed the existence of an underground pipe-line that unintentionally transferred water from the pesticide building to refinery traps resulting in contamination of the soapstock intended for sale as animal feed fat (Firestone, 1978).

Whatever the interest of these accidental contaminations, the episodes of “rice oil disease” that occurred in Japan and Taiwan remained milestones in the history of dioxin-like food-poisoning.

Yusho [Japan, 1968], Yucheng [Taiwan, 1979]

On June 7, 1968, a three-year-old girl with an unusual acne-like eruption was brought to the Kyushu University Hospital. Two months later, 13 patients had been referred to the same hospital with similar cutaneous symptoms. Most patients had an eye discharge and cutaneous lesions made of closed comedones and numerous cysts of various sizes located mainly on the cheeks, auricles, retroauricle areas, inguinal regions and genitalia. Black keratotic masses plugging the follicles were also noted in the armpit, cubital fossa and popliteal space. Concerning the pathological alterations, cystic dilatation of the follicles filled with keratinous masses was observed. The sebaceous glands were atrophic, the horny layer was thin, the basal layer exhibited a marked pigmentation. No change was noted to sweat glands. Hyperpigmentation was observed on nails, gingivae, palpebral conjunctivae and lips. In fact, pigmentation of the oral mucosa was one of the characteristic signs of the disease and persisted for a long time. Radiographic examination of the patients showed anomalies in the number of teeth and in the shape of the roots (Masuda and Schecter, 2012). Swelling of the meibomian glands was conspicuous as a cheese-like mass that could be squeezed out by finger pressure. The ocular signs subsisted up to ten years after the onset of the disease. The content of the tarsal gland was sometimes found to contain PCB (Urabe and Asahi, 1985).

Following these cutaneous and mucous signs, the patients complained of systemic symptoms: loss of appetite, headache, numbness of the limbs, hypaesthesia, asthenia, nausea, swelling of the extremities, dullness, nervous and endocrinological disturbances, respiratory disorders (mainly a persistent cough with expectoration), chronic bronchitis and bacterial infections (Urabe *et al.*, 1979).

Besides the cutaneous and general symptoms, obstetricians observed births with abnormal pigmentation [greyish dark brown] of baby skin, - called “cola coloured babies” - that gradually vanished (Kuratsune *et al.*, 1972). This effect, first reported in a journal with a small circulation, remained initially unknown outside Japan before it was published in an English-language paper in 1971 (Miller, 1971; Miller, 2004; Taki *et al.*, 1969).

The outbreak of this strange disease was made public on October 3, 1968. On October 19, 1968 the local government of Fukuoka Prefecture established the Study Group of Yusho at Kyushu University, in order to identify the causal agent of this disease (Yoshimura, 2003). On January 20, 1969, 325 cases of Yusho had been diagnosed. Most of the patients were located in Fukuoka and Nagasaki prefectures. Half of them had ingested canned rice oil; the other half used bottled rice oil. Among the patients who had used the canned oil, 166 of them had consumed a specific oil produced by the K company on February 5 and 6, 1968. A case control study was carried out and 47 items related to lifestyle were investigated. Only one distinct difference was noted between cases and control, the regular use of rice-bran oil. The Group compared the exposed patients to 131 non-exposed people who used K rice oil regularly except in February 1968. None of these patients had signs of Yusho. The Study Group also identified the individual consumers who used the canned rice oil.

Finally, the Study Group summarized its findings as follows: Yusho incidents occurred in 1968 and peaked in June through August; Yusho had familial aggregation; there were no differences in attack rates among gender and age group; only the regular rice oil was suggested as a possible factor; February's K rice oil had a high risk of 64% compared to zero among non-exposed people; a positive relationship existed between estimated individual amounts of rice oil intake and the severity of Yusho. The authors concluded that Yusho might be caused by the ingestion of the K rice oil produced in early February 1968 at the K company.

Then, further investigations raised the suspicion that possible contaminants in the final product could be responsible for Yusho. However no chemical was detected. In fact, the problem came from the deodorization process for which crude oil had to be heated. During the process, Kanechlor 400® (3,3',5,5'-PCB; KC-400), used for heat transfer, had leaked into the rice oil. The final oil was therefore contaminated with PCB, as confirmed by analysing bottled oil produced in February 1968. However, due to the fact that patients, even those who had the most severe symptoms, had low levels of PCB, the definite responsibility of KC-400 alone was questioned. Moreover, the Study Group failed to reproduce the disease in an animal model. Finally, a significant amount of polychlorinated dibenzofurans [PCDF] - generated by heat denaturation of PCB - in the rice oil consumed and in the tissues of the patients was detected and was considered as the actual cause of Yusho. The oil was found to contain 1,000ppm PCB and 5ppm PCDF. It was also found that the rice oil was also contaminated with polychlorinated quaterphenyls. Regarding the pathogeny of the skin lesions, Urabe and Matsuda hypothesized that the orifices of the hair follicles received a comedogenic stimulus from the PCB and formed the acneiform eruption (Urabe and Asahi, 1985). By 1971, over 1,800 patients were affected with Yusho, the Japanese name for "oil disease".

Since the outbreak of Yusho, the Yusho Group has conducted annual medical check-ups of those involved, consisting of interviews and physical, dermatological, ophthalmological, dental and laboratory examinations.

Two years and ten months after the onset of Yusho, a 48-year-old female died from liver cell carcinoma. From the onset of the disease till 1986, 120 deaths [79 males and 41 females] had been reported. An increased mortality risk for total cancer, liver cancer and lung cancer was observed among male patients. By 1990, 200 Yusho patients had died.

In 2008, Onozuka et al. conducted a 40-year follow-up, retrospective study to evaluate mortality among 1,596 Japanese patients suffering from Yusho and followed until death or the end of the study [December, 31 2007]. Male Yusho patients showed an elevated mortality rate from all types of cancers, liver cancer and lung cancer in particular, in comparison with the general population (Onozuka *et al.*, 2009). Skin lesions had vanished slowly over three or four years, though sometimes more [five to six years for the comedones.] Many patients showed ice-pick scars. Fifteen years after the onset of the disease, cutaneous lesions were usually slight and the systemic symptoms absent. As regards the "cola coloured babies", it was shown that PCB and PCDF were transferred from poisoned mothers via the placenta and breast milk. Seven years after the exposure,

13 children (were dull with?) were found to have low IQs. The blood concentrations of PCB and dioxins decreased over 40 years. However, in 2007 it was shown that the blood levels of 2,3,7,8-PCDF remained 11.3 times higher than those of controls.

In 2012, an examination of the skin symptoms of 352 Yusho patients [185 males and 167 females] was performed. Black comedones, acneiform eruptions and scar formation were still observed in one-third of the patients. Forty-four years after the outbreak of the disease, the mean PCDF blood level was eight times higher than normal levels. A significant correlation was found between the severity scores of black comedones and 2,3,4,7,8-PCDFs and PCB blood levels (Mitoma *et al.*, 2015).

Despite the onset of Yusho ,in 1968, PCBs were not immediately regarded as toxic as the production increased in Japan in the two following years. The production and use of PCBs in Japan were prohibited in 1972 (Masuda, 2003).

A similar episode [namely Yucheng, a Chinese word for rice oil disease] occurred in Taiwan eleven years after Yusho. On May 21, 1979 the Hui-Ming School for the Blind reported the occurrence of strange acne-like eruptions. As in Yusho, Taiwanese patients had consumed rice oil from the same origin manufactured by C-Company, and this oil was suspected of containing the causal agent. In September 1979, two more companies reported that approximately 100 workers were suffering from the same disease. All of them had consumed C-rice oil. PCB contamination was proved in October 1979 and the oil removed from the market. The C-rice oil contained KC-400 was also contaminated by PCDFs and polychlorinated quaterphenyls. It has been estimated that the total intake by the victims of poisoning was about 1g of PCBs and 3.8mg of PCDFs. The patients were mainly workers from three factories and students from the School for the Blind. In the first year of the outbreak, about 41% of the patients showed symptoms of mild severity - i.e. an increased cheese-like discharge from meibomian glands and pigmentation of nails - and 26% had symptoms of moderate severity - i.e. the same symptoms plus comedones.

An epidemiological survey revealed that1,843 cases reported from December 1978 to November 1980 and 2,061 cases reported in 1985, including 39 infants, showed hyperpigmentation. Among these infants, between 1980 and 1983, eight died from premature birth, pneumonia and sepsis. Another 24 deaths were reported in adults between 1980 and 1983 (Hsu *et al.*, 1985).

In 1985, Rogan et al. conducted a survey of all living children who had been *in utero* during or after the period of oil contamination. One hundred and seventeen children were compared with siblings born before the toxic episode. Of the exposed children, 10% had a developmental or psychomotor delay (Rogan *et al.*, 1988). They were smaller than the controls and had more abnormalities of the gingiva and teeth. Neither acne nor conjunctival cysts were more common in the exposed group. At birth, exposed children had increased rates of hyperpigmentation, acne, deformed nails and swollen eyelids. Gladen et al. studied 128 children born as late as 1985, transplacentally exposed to PCBs and PCDFs and compared them to 115 control children. Multiple neonatal findings were noted by parents: swollen eyelids, white eye discharge, hyperpigmentation,

deformed nails, acne, natal teeth and swollen gums. Seventy-five children had at least one of the abnormalities, 50 had multiple findings. Acneiform lesions were twice as common in the transplacentally exposed children as in the control group. They also noted more generalized itching and localized skin infections (Gladen *et al.*, 1990; Ryan, 1993).

Six years after the establishment of the 1985 cohort, Hsu et al. conducted a similar survey to follow-up the dermatological findings. Eighty-eight exposed children and 86 control children were examined. Among the dermatological findings, the nail alterations were prominent: transverse grooves [the most significant nail change between exposed and non-exposed children], irregular depressions, punctuate pits, koilonychia and transverse lines were observed. Comedones, pitting scars, scratch scars and xerosis were also observed in affected children. The frequency was however not significant when compared to the non-exposed children. The authors concluded that eleven years after the Yucheng outbreak, the skin or mucosal pigmentation and the meibomian gland manifestations initially observed were no longer present. Hsu et al. pointed out that chloracne and partial pigmentation occurred mainly in adults directly exposed to the chemical whereas generalized pigmentation [cola coloured baby], meibomian gland enlargement and nail alterations are the consequences of congenital exposure (Hsu *et al.*, 1995).

Fourteen years after the onset of Yucheng, Guo et al. obtained informations from some 800 exposed subjects. Compared to some 700 non-exposed people, lifetime prevalence of chloracne was 15.4% of the exposed men (compared to 1.3% in control men) and 19% of exposed women (1.3% in control women); abnormal nails were found in 10% of the exposed men (1.3% in controls); hyperkeratosis found in 5% of exposed women (1% in control women); goitre, headache, gum pigmentation in 6.3% of the exposed women (1.3% in control women) and gum swelling and broken teeth were observed more frequently in PCB/PCDF exposed men and women. Skin allergies occurred approximately twice as frequently in the exposed group. The authors did not find any increased cancer mortality rate in the Yucheng cohort as had been found in Japan (Guo *et al.*, 1999).

Additional episodes of food contamination

In 1973, approximately 1,000 to 2,000 pounds of toxic fire retardants, i.e. hexa-, octa- and decabrominated biphenyls [Firemaster BP-6®, Bromkal®, Flammex®] were inadvertently mixed in a factory of the Michigan Chemical Corporation, with animal feed [Nutrimaster®] for dairy cattle. About 30,000 cattle died or had to be killed. Until the affected food products were quarantined in spring 1974, about 10,000 Michigan residents were exposed to PCBs through consumption of dairy products and meat (Landrigan *et al.*, 1979).

In summer and autumn 1974, the Michigan Department of Health studied the human effects of the event: no unusual abnormalities of the heart, liver, nervous system, (blood control, urine analysis) were found in 300 exposed people who had worked or lived in the quarantined farms for six months or more after the accident. Normal babies were delivered by exposed women (Reggiani

and Bruppacher, 1985). In a retrospective study Chanda et al. listed the skin lesions observed eight years after the Michigan event among quarantined and non-quarantined farm workers, plant workers and in a control group. Diffuse alopecia was observed in 4% of the combined quarantined and non-quarantined farm groups compared to none in controls. Chloracne was observed among 13% of the plant workers compared to 2% among the quarantined farm workers and 5% among the non-quarantined. Chanda et al. pointed out that bromacne was the only sign of exposure in those with the highest PCB blood levels (Chanda *et al.*, 1982).

In September 1982, the members of a family were examined at the Dermatologic Clinic in Seville Hospital. The father, the pregnant mother, the sons and daughters were affected with chloracne that had appeared one or two months before. Enquiries revealed that the family had stocked olive oil in plastic containers that had been used for other uses previously. Analysis revealed the oil contained hexachlorobenzene, PCPs and traces of polychlorinated dioxins. The younger members of the family recovered in few months after the exposure had been discontinued. Five years after the occurrence of chloracne PCDDs and PCDFs were detected in blood samples from the family (Rodriguez-Pichardo and Camacho, 1990; Rodriguez-Pichardo *et al.*, 1990).

Between January 19 and January 26, 1999, a serious sanitary incident occurred in Belgium called the "crisis of dioxin" or "chicken gate" due to the contamination of animal food by animal fat in which transformer oils containing PCBs [Aroclor®] were accidentally or intentionally incorporated. No symptoms were observed in humans during the period of the crisis. This dioxin incident cost the Belgian Treasury in excess of 1 billion euros, the Minister of Agriculture had to resign, followed by the Minister of Health and eventually the entire Belgian government collapsed. Three years later, due to the absence of any exhaustive epidemiological study, Focant et al. failed to provide a proper evaluation of the crisis on consumers' health (Focant *et al.*, 2002; Koppe and Keys, 2002). Bernard et al. expressed similar views (Bernard *et al.*, 1999). Piérard et al. stressed the role of the media that instrumentalised the event to give it the importance of a "surrealistic catastrophe" despite the reassuring advice of experts and sanitary agencies (Piérard *et al.*, 2005).

In the US, in 1997, chickens, eggs, and catfish were contaminated with dioxins when tainted clay was used in the manufacture of animal feed. The contaminated clay was traced to a bentonite mine. As there was no evidence that hazardous waste was buried at the mine, investigators speculated that the source of dioxins might be natural, perhaps due to a prehistoric forest fire.

Unusual elevated TCDD levels were not necessarily associated with internal organ manifestations, as shown by the cases published by Geusau et al. In October 1997, a 30-year old woman developed acneiform eruptions accompanied by general symptoms [nausea, vomiting and fatigue] after she moved into a new office space at a textile institute in Vienna. Six months later, the patient and a colleague were seen at the Department of Dermatology with severely inflamed acneiform eruptions quite close to acne fulminans. The dermatologists confirmed the diagnosis of chloracne and detected the highest TCDD value ever recorded in a human : 144,000pg/g blood fat that corresponds to a body burden of 1.6mg TCDD and a dose of 25µg/kg body weight. The TCDD

blood level of the second patient working in the same company was 26,000pg/g blood fatty. Elevated TCDD blood levels were also found in 3 of the 30 employees working in the same institute who did not developed chloracne. The authors hypothesized a food origin as the patients suffered with chloracne and minor gastrointestinal symptoms only. No serious manifestation in other organs was noted (Geusau *et al.*, 2001). Both patients were treated by olestra - a non-digestible, non-absorbable, dietary fat substitute - over 38 days with 5 different dosing regimens each of them lasting 7 days. The intestinal excretion of TCDDs was increased by eight to ten fold. The elimination half lives due to faecal excretion alone were 1.4 years in the first patient and 1.9 years in the second, therefore below what is regarded as the usual TCDD half life, i.e. about 10 years (Geusau *et al.*, 1999). Two years later, the chloracne had progressed in the first patient, the whole skin being covered with inflamed cysts. Moreover, additional cutaneous lesions were observed: hypertrichosis of the limbs, granuloma annular-like lesions, brownish-grey hyperpigmentation, partial onycholysis and punctate keratoderma-like lesions on the palms and soles (Geusau *et al.*, 2000). Contrasting with the worsening of the cutaneous symptoms, no routine biological alteration indicated dioxin poisoning three years after the onset of the disease. The second patient exhibited only mild chloracne (Geusau *et al.*, 2002). After seven years, the first patient, treated with systemic corticosteroids for two years, was significantly improved. Apart from mild cutaneous symptoms, no sign of TCDD was noted in either of the two patients (Geusau and Abraham, 2005).

In March 1998, high levels of dioxins in milk sold in Germany were traced to citrus pulp pellets used as animal feed imported from Brazil (Focant *et al.*, 2002). In 2004, elevated levels of dioxins in milk from The Netherlands resulted in the discovery of a serious contamination of feed with dioxins coming from kaolinitic clay. In July 2007, high levels of dioxins were detected in guar gum used in small quantities as a thickener in meat, dairy products and desserts. The source was traced to guar gum from India that was contaminated with PCPs. Elevated dioxin levels were also detected in animal feed in The Netherlands in 2006.

In 2007, a “mozzarella crisis” occurred in Italy. As reported by various articles “high levels of dioxins have been found in buffalo milk in a group of dairies in Campania, the southern province centring on Naples where most mozzarella production takes place. Italy's public health authorities believed that the contamination was the result of illegal dumping of toxic waste in Campania, where the waste industry is under the control of the Camorra, the local branch of the Mafia, and where Naples and its region are undergoing a major waste management crisis” (McCarthy, 2008).

In early December 2008, contaminated animal feed distributed by one Irish manufacturer to thirty-seven beef farms and nine pig farms across the Republic of Ireland and eight beef farms and one dairy farm in Northern Ireland, caused the contamination of pigs with 80 to 200 times the EU’s recommended limit for dioxin and dioxin-like compounds. The contaminated feed was judged to have caused no significant public health risk (Kennedy *et al.*, 2009). More recently, a fraudulent food contamination was suspected of as causing cases of chloracne observed by Passarini et al. The

authorities hypothesized that somebody contaminated foods that a farmer left every week for the patients who inhabited the same building (Passarini *et al.*, 2010).

Chloracne : elusive effect of Agent Orange in the Vietnam war

From 1961 to 1971, so-called tactical herbicides were sprayed over South Vietnam by the US army. Among them, Agent Orange - that contained a mixture of 2,4-D and 2,4,5-T (and TCDD as a contaminant) - was extensively used. A few years after the onset of the spraying, deleterious ecological effects and possible adverse effects on human health were pointed out. As various general symptoms and illnesses, including chloracne and possible cancers, had been previously observed or suspected after occupational exposure, industrial accidents or food contamination involving dioxin, Vietnam veterans exposed to Agent Orange suspected the symptoms they exhibited to be related to dioxin exposure. Numerous epidemiologic studies were then conducted to assess the responsibility of the chemicals. Despite the controversies and the inconclusiveness of most of these studies, several diseases, including chloracne were retained for veterans compensation.

This fascinating history that highlights the links between chloracne and herbicides, originates with contributions of French, German and US viticulturists.

From domestic to tactical uses of herbicides

In the 1880s viticulturists observed that copper salts [Bordeaux mixture, French “bouillie bordelaise”] and various inorganic compounds could kill broadleaf weeds but not cereals growing in the vicinity (Burnside, 1996; Butler, 2005). Following these observations, chemists endeavoured to isolate molecules than could be useful in agriculture. In 1926, Went isolated from plant tissue, indoleacetic acid [IAA], a growth controlling substance initially called a hormone due to the fact it could act like hormones in animals, later designated an “auxin”. It was then discovered that naphtylacetic acid [NAA] could also kill certain broad-leaved weeds in cereals without harming the grain crops. These compounds were, however, too expensive and too quickly degraded by microorganisms in the soil to be of practical agricultural use. In the 1940s, three teams of chemists synthesized chemicals that became widely accepted in agriculture. The International Chemical Industry [ICI] chemists and, independently, researchers at the Rothamsted Experimental Station isolated phenoxyacetic acid (Troyer, 2001). In 1941, Pokorny [chemical company CB Dolge] authored the first scientific publication that mentioned 2,4-D and 2,4,5-T. In February 1942, Jones [American Chemical Paint Company] came to a similar discovery while researching ways “to find a compound to kill poison ivy, motivated not only by commercial interests, but also by the fact that his children were highly sensitive to the poisonous plant” (Jones, 1942).

The effectiveness of 2,4-D and 2,4,5-T resulted in their rapid acceptance in agriculture. 2,4-D was patented in the US on December 11, 1945 and introduced commercially a year later. 2,4,5-T became extensively used in farming, forest management, family gardens and weed control along roadsides and railroad rights-of-way. Its production in the US dramatically increased from 2,400t in 1958 to 19,000t ten years later (Firestone, 1978).

In 1941, Kraus, Chairman of the Botany Department of the University of Chicago's, suggested that the toxic properties of these substances should be investigated for military purpose. In this respect, Secretary of War Henry Stimson asked the National Academy of Sciences (NAS) to assess the state of knowledge of biological warfare. In November 1942, the US Army began developing Camp Detrick [later renamed Fort Detrick] in Frederick, Maryland, as the centre for research on biological warfare, with special emphasis on crop-destroying chemicals.

The University of Chicago was then contracted to study the effects of various organic compounds on cereal grains and broadleaf crops. Of the more than 1,000 potentially useful agents tested in the Florida Everglades, 2,4-D and 2,4,5-T were the most promising. Herbicides were actually not used in the military during WWII. They were used for the first time as a weapon by British troops between 1951 and 1953, during the

"Malayan Emergency" that attempted to overthrow the British administration in Malaysia. Then, the US Army Chemical Corps Biological Laboratories at Camp Detrick developed aerial spraying equipment and a herbicide formula for possible use in the Korean conflict. Herbicide research funding at Fort Detrick ended in 1958. The remaining stock of 2,4-D and 2,4,5-T was used in June 1959 to clear vegetation at Fort Drum, New York.

Operation "Ranch Hand" in Vietnam; military aftermath of herbicide use

Briefly summarized, after France had begun its colonization of Indochina in the 1850s, numerous opponents to French rule appeared during the 19th and 20th centuries. After the end of WWII, the Viet Minh and its leader Ho Chi Minh continued the fight for independence from France and against the Japanese occupation of Indochina. On September 2, 1945, Ho Chi Minh declared the formation of the Democratic Republic of Vietnam recognized in January 1950 by the Soviet Union and the People's Republic of China [PRC] as the only legitimate government. Despite the support of the US, France failed to resist the Viet Minh opposition and finally the French army was defeated at Dien Bien Phu on May 7, 1954.

Following the Geneva conference held after Dien Bien Phu, Vietnam was partitioned at the 17th parallel, the North Vietnam - Democratic Republic of Vietnam - communist regime governed by the Viet Minh and the southern part constituted as the Republic of Vietnam. Ngo Dinh Diem, an anti-communist and nationalist, was installed as Prime Minister of the Republic of Vietnam and was

supported by the US in order to stop the spread of communism over Southeast Asia, according to the "domino theory". During a 300-day provisional period, Vietnamese people were allowed to move freely between the two parts of the country. In 1961, John F Kennedy took office in Washington DC and confirmed the military and economic assistance provided by the US to the South Vietnamese government.

Birmingham recalled that the decision that led to sending aircrafts equipped with spraying equipment to South Vietnam had begun on April 12, 1961 with a memo from Walt W. Rostow, foreign affairs advisor to President Kennedy. He suggested that a development team went to Vietnam and explored the usefulness of various "techniques and gadgets" available: "the President has approved the recommendation of the Secretary of State and the Deputy Secretary of Defense to participate in a selective and carefully controlled joint program of defoliant operations in Vietnam starting with the clearance of key routes and proceeding thereafter to food denial only if the most careful basis of resettlement and alternative food supply has been created." Aerial defoliation became one of these "gadgets". The operation was dubbed "Operation Ranch Hand", the military code name for the spraying of so-called "tactical herbicides" from US Air Force aircrafts. The designation had actually no particular significance and was one of a number of similar code names such as *Farm Gate and Barn Door* (Buckingham, 1983). A South Vietnamese Air Force H-34 helicopter flew the first defoliation test mission in South Vietnam on Thursday August 10, 1961 using the herbicide dinoxol, a mixture containing 32% of 2,4-D-butoxyethylester and 30% of 2,4,5-T-butoxyethylester as active ingredients. Two weeks later, the first fixed-wing spray mission occurred along Highway 13 north of Saigon.

As the situation in South Vietnam worsened, in autumn 1961, the possibility of securing South Vietnam's borders against infiltration from North Vietnam was discussed. Defoliation operations were one of the proposed actions that could be carried out to remove the vegetation cover used by the Vietcong – the South Vietnamese communist movement opposed to Diem's regime and that was provided with weapons and materials by the Democratic Republic of Vietnam - and North Vietnamese forces for concealment. The Combat Development and Test Centre [CDTC] developed a program that included "stripping the Cambodian-Laotian-North Vietnam border of foliage to remove protective cover from Vietcong reinforcements; defoliating a portion of the Mekong Delta in which the Vietcong have numerous bases; destroying numerous abandoned manioc groves which the Vietcong use as food sources; destroying mangroves swamps within which the Vietcong take refuge". The program that actually proposed the defoliation of about half of South Vietnam, had a cost of $75 million to $80 million and exceeded the chemical manufacturing capacity in the US. A revised defoliation program was therefore proposed, estimated at $4 million to $6.5 million.

The US Air Force sprayed 95% of the tactical herbicides in Operation Ranch Hand from December 29, 1961 to October 31, 1971, mainly from Fairchild C-123 aircrafts (Young, 2009). Smaller quantities were applied from helicopters, trucks and riverboats and by hand. The spray fell mostly on South Vietnam, but some was used in Laos.

Three major herbicides were sprayed: Agent Orange [a reddish-brown coloured liquid containing a 1:1 mixture of 2,4-D and 2,4,5-T, 43,330,640 litres of which was sprayed from 1965 to 1970], Agent White [a dark-brown viscous liquid containing a 4:1 mixture of 2,4-D and picloram (4-Amino-3,5,6-trichloro-2-pyridinecarboxylic acid), 21,798,400 litres of which was sprayed from 1966 to 1971] and Agent Blue [dimethylarsinic acid or cacodylic acid, commercially known as Ansar 138®, 6,100,640 litres of which was sprayed from 1966 to 1971] (Stellman and Stellman, 2005). To identify them, the 208-liter [55-gallon] drums were color-coded with a 7.6 cm band painted around the centre of each drum. The herbicide contained in drums with orange stripes became Agent [or Herbicide] Orange. It was first introduced in South Vietnam on March 1965. Ninety per cent of it was used for forest defoliation, especially the mangrove forests. It was purchased from chemical companies [Dow Chemical Co., the main provider, Monsanto Co., Hercules Inc., Thomson-Hayward Chemical Co., Diamond Alkali/Shamrock Co., US Rubber Co., Thomson Chemicals Corp., Agrisect Co., and Hoffman-Taff Inc.] which provided the Department of the Army with 249,960 drums, 195,000 of which were provided by Dow Chemical Co., Monsanto and Hercules Inc.

Besides these agents, three other colour-codes were used : Purple [2,4-D and 2,4,5-T, 2,580,240 litres sprayed from 1962 to 1965], Pink [2,4,5-T, 235,040 litres sprayed from 1962 to 1963] and Green [2,4,5-T, 75,920 litres sprayed in 1962]. Agents Purple and Blue were received in Vietnam on January 9, 1962; they were the first herbicides used in Operation Ranch Hand.

The quantity of herbicides sprayed by the US forces during the Vietnam War has been estimated at about 19,900,000 gallons or 75,322,000 litres, containing between 170 kg and 180 kg of dioxin on approximately 5 million acres [or 2 million hectares] of Vietnamese and Laotian land. Vietnam was the first country in which defoliants were used on such a large scale only to achieve military objectives.

Although the exact number is not known, according to the Veterans' Association (VA), it is theoretically possible that about 4.2 million American soldiers could have made transient or significant contact with the herbicides (Zumwalt, 1990). However, for other authors, although approximately 1,200 Ranch Hand workers were exposed to herbicides, there are no data on the number of non-Ranch Hand individuals who may have been exposed to Agent Orange or other herbicides (Young, 1981a).

After the defoliation program had been discontinued, approximately 8.7 million litres of Agent Orange were placed in storage at the Naval Construction Battalion Centre at Gulfport, Mississippi and on Johnston Island in the Pacific Ocean. Numerous methods for disposing of the herbicides were evaluated. Finally, the remaining drums were incinerated at sea aboard a specially designed Dutch incineration vessel, the "Vulcania" in a remote area west of Johnston Island ([Anonymous], 1977). The operation was completed in September 1977.

First concerns and controversies

According to Butler, two events changed the opinion with regard to the safety of herbicides sprayed over Vietnam (Butler, 2005). In 1965, the National Cancer Institute had awarded a contract to Bionetics Research Laboratory to conduct carcinogenicity, mutagenicity and teratogenicity tests on various pesticides. The publication of the results, in February 1969, that showed that 2,4,5-T ingested or injected could cause birth defects in mice and rats has been regarded as the birthdate of the Agent Orange history as a matter of public concern (Courtney *et al.*, 1970; Kotin *et al.*, 1968; Meselson *et al.*, 1970; Reggiani, 1988a). Later analysis of the chemical revealed, however, that 2,4,5-T was not teratogenic in itself; only its contaminant TCDD was. The second event was the publication from June 26 to July 5, 1969 of South Vietnamese newspapers that reported an increased rate of birth defects. Although some authors had suggested that the increase was actually apparent due to the influx of American doctors into the Saigon area that might have had a positive impact on better record keeping, following these events, the White House ordered a curtailment of the use of Agent Orange in Vietnam on October 29, 1969 (Meyers, 1979).

Meanwhile, additional reports were reassuring about the health effects of herbicides on humans and animals, in spite of their deleterious ecological consequences.

In 1967, the Department of Defense [DoD] contracted with House et al. from the Midwest Research Institute [MRI] for an extensive report on the safety of the tactical herbicides on animals and humans. After reviewing more than 1,500 articles and books and interviewing over 140 people, the authors expressed reassuring views about the toxicity of herbicides on humans: "[1] the direct toxicity hazard to people and animals on the ground is nearly non-existent, [2] destruction of wildlife food and wildlife habitat will probably affect wildlife survival more than any direct toxic effects of the herbicides, [3] the application of Orange or White agents alongside the rivers and canals and even the spraying of the water area itself at the levels used for defoliation is not likely to kill the fish in the water, [4] food produced from land treated with herbicides will not be poisonous or significantly altered in nutritional quality; if residues of a more persistent herbicide such as picloram should carry over to the next growing season it would retard plant growth rather than concentrate some toxic residues in the crop, [5] toxic residues of these herbicides [Orange, White and Blue] will not accumulate in fish and animals to the point where man will be poisoned by them, and [6] the primary ecological change is the destruction of vegetation and the resulting ecological succession in the replacement of this vegetation" (House *et al.*, 1967).

Following these statements, in September 1968, the US Department of State released an assessment of the effects of the defoliation program in South Vietnam. Conducted by Tschirley, a plant ecologist, after a four-week visit to South Vietnam, the study concluded that "the herbicides used in Vietnam are only moderately toxic to warm-blooded animals. None deserves a lengthy discussion except for Agent Blue [cacodylic acid] which contains arsenic […] There is no evidence to suggest that the herbicide used in Vietnam will cause toxicity problems for man or animals. […] the defoliation program has caused ecological changes […] not irreversible, but complete recovery

may take a long time. […] Regeneration of the mangrove forest to its original condition is estimated to require about 20 years" (Tschirley, 1969).

A complementary trip of two zoologists sponsored by the Society for Social Responsibility in Science in March 1969 confirmed "the profound effects of denuding the country of growth." By contrast, the zoologists "uncovered little evidence of direct toxic effects on animals" (Orians and Pfeiffer, 1970).

The article published by Rose and Rose in 1972 contrasted with the previous ones. It not only mentioned the ecological changes but also the effects on humans. From December 1970 to January 1971, in Hanoi, with the cooperation of Vietnamese physicians, they interviewed 98 refugees from South Vietnam who came from sprayed areas. Most of them reported reddening or inflammation of the eyes or even temporary loss of vision after they had inhaled the spray. Five percent of them reported that their sight was permanently "dimmed". Skin burning occurred in 56 % of the exposed people whereas 16% reported persistent pustules and eczema. Most of these initial symptoms occurred within the three hours following the spraying of the defoliants. Fatigue, weariness and dizziness were also mentioned by 92 % of the people interviewed (Rose and Rose, 1972).

In fact, the ten-year retrospective survey of the records of 22 hospitals conducted by the US Army Medical Research Team in Vietnam, the Ministry of Health of Vietnam and the Office of the Command Surgeon in Vietnam generated the main interest. The investigators pointed out that the study did not intend to test a relationship between herbicides and birth abnormalities that would have necessitated prospective studies and the comparison between comparable populations exposed and not exposed to the herbicides. Moreover, the authors also admitted that their study had several biases: nearly all information came from large hospitals, the data from private medical sources were absent and the data were almost completely limited to ethnic Vietnamese. Keeping these limits in mind, sorting the data into two periods, before 1960 to 1965 [light-spraying years] and after 1966 to 1969 [heavy-spraying years], the survey failed to show any negative effect of the large scale military use of herbicides. Rather, a downward trend of abnormal birth events was observed. Finally, when comparing the rates of stillbirth, malformation and moles, the authors concluded that the rates were within the ranges reported for other Asian populations (Cutting *et al.*, 1970).

In the same period, the American Association for the Advancement of Science [AAAS] established a commission to assess the effects of large-scale use of herbicides in South Vietnam. After touring in the country, the members of committee concluded - as ecologists and scientists previously had - that the herbicides had destroyed the vegetation and the food needed by the population. They considered, however, that "the studies of changing rates of stillbirths, particularly as reported by the government maternity system are subject to great errors of interpretation […] Although the reported rate of stillbirths in Tay Ninh province - extensive areas of which were treated by 2,4,5-T - are higher than the highest provincial rates […], this type of evidence is not sufficient to draw any firm etiological conclusion" (Meselson *et al.*, 1972).

“Because of [these] uncertainties”, on April 14, 1970, the Secretary of Health, Education and Welfare [HEW] advised the Secretary of Agriculture “that the Surgeon General feels that a prudent course of action must be based on the decision that exposure to [this] herbicide may present an imminent hazard to women of child-bearing age.” On the following day, the Department of Health, Education and Welfare ordered an immediate halt to the use of this substance in the US. The Department of Defense stopped spraying Agent Orange on the same day. This was followed by the cancellation of all registered uses of 2,4,5-T for certain food crops.

A few days later, manufacturers, including the Dow Chemical Company, the primary manufacturer of 2,4,5-T and 2,4-D,, denied these adverse effects and exercised their rights under the Federal Insecticide, Fungicide and Rodenticide Act to appeal the cancellation order (Aaronson, 1971). In 1972, Dow Chemical obtained a temporary court injunction preventing the EPA from taking further action against 2,4,5-T. The following year, this was overturned by the US Court of Appeal. The EPA considered that available data on the effects of 2,4,5-T and TCDD on humans in exposed areas were inconclusive and refused to rescind the cancellation order.

Meanwhile, several events that occurred outside the US heightenedconcerns about herbicides.

In 1969, the US Forest Service applied Silvex [Fenoprop; 2-(2,4,5 trichlorophenoxy) propionic acid] in the Kellner Canyon-Russell Gulch near Globe, Arizona. Immediately after the spraying, complaints were reported of animal and human illnesses. The investigation conducted by the Office of Science and Education confirmed the absence of significant effects on animals. Regarding human diseases, it was concluded that the complaints were those observed in the normal population; no case of chloracne was reported.

In the spring of 1970, numerous deaths of reindeer grazing in Lapland were reported by Swedish newspapers. The event attracted attention due to the fact that the area had been previously sprayed with 2,4-D and 2,4,5-T. Following the reports of animal deaths, two cases of congenital malformation in human infants were attributed to alleged exposure of pregnant women during the spraying of phenoxy herbicides. The Institute of Hygiene and the (teratological laboratories?) in Stockholm could not confirm that the occurrence of these birth defects was more than coincidentally related to defoliating operations.

An episode similar to that in Swedan occurred in 1972, in Te Awamutu, New Zealand. Two babies from two families were born with defects incompatible with life. The families lived in farms where, for several years, spraying of 2,4,5-T had been carried out. After investigation, it was concluded that in one of these cases the exposure to 2,4,5-T had not caused the defects. For the second case, no definite conclusion could be obtained. In 1977, 20 additional cases of birth defects were suspected of being linked to use of 2,4,5-T. Finally, it was admitted that phenoxy herbicides had no responsibility in the occurrence of malformations in animals or in humans.

In this context of controversy, the US Congress directed the Secretary of Defense “to enter into appropriate arrangements with the NAS to conduct a comprehensive study and investigation to

determine [A] the ecological and physiological dangers inherent in the use of herbicides and [B] the ecological and physiological effects of the defoliation program carried out by the Department of Defense in South Vietnam" ([Anonymous], 1971a). The NAS then formed an Advisory Committee which had to "consider all relevant facts, submit a report and recommendations regarding registration for certain uses of 2,4,5-T and state the reasons or bases for these recommendations."

Reassuring statements, additional concerns

The NAS Committee concluded that "competent medical and agricultural experts have been unable to find evidence of adverse effects on either human or animal reproduction that could be attributed to the defoliants." When examining the Vietnamese data on human embryotoxicity, the Committee considered that the "sample of births surveyed […] was quite unrepresentative of the geographic and ethnic distributions, […] the birth records were not trustworthy and therefore the rates of stillbirth and especially of congenital malformations derived from them were equally unreliable. […] Finally there is, and can be, no precise knowledge or reasonable approximation of the exposure to 2,4,5-T by pregnant Vietnamese women including what amounts they ingested or absorbed and when this may have occurred during pregnancy. Thus any attempt to relate birth defects or stillbirths to herbicide exposure is predestined to failure. It can only be concluded that the birth records that have been surveyed […] for South Vietnam for the period 1960 to 1970 cannot answer positively the questions about possible adverse prenatal effects following human exposure to 2,4,5-T." Finally, the Committee concluded that "as presently produced and as applied according to regulations in force prior to April 1970, 2,4,5-T represents no hazard to human reproduction." Disagreeing with this statement, a member of the committee – Professor T.D. Sterling, Department of Applied Mathematics, Washington University, Saint Louis, Missouri , pointed out that the "the report fails to consider the consequence of the uncertainty about the fate of TCDD in the food chain in tissue" and regarded "the report [as] overoptimistic in assessing the implications of the data so that it may well underestimate what dangers may lurk in the unrestricted use of 2,4,5-T" ([Anonymous], 1971b).

In 1974, the NAS published the results of the studies conducted in South Vietnam in 1972 and 1973 and stated that "available records of two major Saigon hospitals and evaluation of records in a third, as far as they go, showed no consistent pattern of association between rates of congenital malformations and annual amounts of herbicides sprayed. The Committee recognizes however that the material is not adequate for definite conclusions" ([Anonymous], 1974).

In March 1975, the EPA released a "Dioxin Implementation Plan" to carry out studies on various foods [beef, milk, catfish] produced in areas where 2,4,5-T was used. Meanwhile, the Council for Agricultural Science and Technology had taken the position that the amount of TCDD present in 2,4,5-T is not enough to endanger human health or affect plants and animals in the

environment. Finally, a Dow Chemical spokesman concluded that “if, with all the confidence we have on the safety of 2,4,5-T, we can’t say it is safe, then we can’t prove the safety of aspirin”.

By contrast with these relatively reassuring statements, several publications alerted the medical and non-medical communities to the adverse effects of Agent Orange and other tactical herbicides.

After the defoliation program ended, Tung et al., from the Department of Surgery in Viet-Duc Hospital, Hanoi, reported an increase in liver cancer in South Vietnam in the late 1960s. While they had observed 26 cases per year between 1955 to 1961, they noted 144 cases per year between 1962 to 1968. According to the authors, this increase was related “to the huge quantity of dioxin sprayed by the US Army over South Vietnam. […] the evidences [they] had accumulated had to draw the attention of the scientific community to this substance massively sprayed over Vietnamese forests the adverse effects of which seem far more severe than those provoked by the already known pollutants” (Tung *et al.*, 1973). Tung however admitted that the increased incidence of hepatocarcinoma observed in South Vietnam might be the result of the number of cases referred to him personally more than the consequence of herbicide exposure.

In 1978, Tung et al. conducted a survey of 903 civilians from South Vietnam who had moved to North Vietnam. Among these, 179 of them, exposed to the spraying of herbicides, related the symptoms that had occurred in the following hours: “as soon as the chemical fog falls down, the patient complains of stinging in the eyes, watering and intense rhinorrhoea; a rough odour of chlorine or of DDT fills his throat while a strong feeling of warmth similar to that of pepper goes up the nose. The patient continuously sneezes, complains of headaches and intense fatigue. […] All these symptoms vanish after 24 hours but the patient feels really better only three to four days later”. *[transl. G Tilles]* The authors also described the birth of children with congenital abnormalities - two of them had Down’s syndrome and one exhibited foot and cognative abnormalities – to mothers who lived, while pregnant, in an area subjected to daily sprayings of herbicides. As regards teratogenicity, the authors admitted that the results previously obtained from animals could not be transposed to humans.

The Dow Chemical Company, the main provider of Agent Orange, denied Tung’s conclusions: “trying to correlate cause and effect from the published data is completely frustrating and futile. There is no doubt that these authors saw some ill people but to reach the conclusion that their problems were caused by 2,4,5-T rather than ravages of war is speculation.” Grummer [Rostock University, German Democratic Republic] also claimed to have observed a high incidence of children with Down’s syndrome while touring through North and South Vietnam. According to him, it might be assumed that “there are at least 25,000 children with hereditary defects in South Vietnam. This does not include all the unborn babies whose mothers were sprayed during the missions that were flown in recent months” (Young *et al.*, 1978).

Additional events supported the anxiety with regard to the noxious effects of dioxins. In 1978, spraying of 2,4,5-T and Silvex in the Alsea basin of Oregon was suspected of being responsible for numerous spontaneous abortions. At the request of the concerned women, the EPA conducted a

preliminary study [Alsea I]. The EPA concluded that there was a seasonal variation in the miscarriage rate among Alsea women compared with a control group from the nearby city of Corvallis and failed to find conclusive evidence of a relationship between miscarriages and 2,4,5-T spraying. However, a more detailed study, called Alsea II, suggested a relationship between 2,4,5-T and an increase in miscarriages. Although the EPA had admitted that "it was practically impossible to do a precise reckoning of the risks and benefits of the herbicide", the alleged miscarriages were regarded as an "alarming correlation [that came] at a time when seven million pounds of 2,4,5-T are about to be used to control weeds". In these circumstances, in 1979, the EPA issued an emergency suspension of all remaining uses of 2,4,5-T except for rangeland clearing and rice field weed control (Cookson, 1979; Hay, 1979). Both studies [Alsea I, II] came under severe criticism due to issues regarding their methodology (Beljan *et al.*, 1984).

An investigation was conducted in 1979 by the NIOSH after a large number of birth defects had been reported among the children of 1,400 maintenance workers of the Long Island exposed to 2,4,5-T. It was found that, of 170 live births, there were actually fewer than the expected number of all major defects combined, but a significant increase of minor defects.

In 1980, a survey by questionnaire was conducted in New Zealand among professional sprayers and their wives, who were also involved in the use of phenoxy herbicides. The survey failed to find any evidence that 2,4,5-T adversely affected pregnancy outcomes (Tindall, 1985).

Veterans' claims

The first reports of veterans' concerns about the health effects of 2,4,5-T began in late 1977 when Maude DeVictor, a benefits counsellor in the Chicago regional office of the VA, was contacted by the wife of a Vietnam veteran, named Charles Owen, who had died from cancer he thought had been caused by exposure to Agent Orange. After the VA had refused his widow's claim for benefits, DeVictor carried out research on the possible adverse effects of herbicides. Then "she was asked [by the VA] to cease […] and concentrate on her assigned duties, but she continued her research on Agent Orange." Soon after someone contacted Bill Kurtis, a local television reporter, about DeVictor's inquiries. […] On March 23, 1978, WBBM, a CBS affiliate in Chicago, aired Kurtis' documentary "*Agent Orange, the deadly fog".* Kurtis concluded the documentary stating that "officially the VA is denying the claims of poisoning by Agent Orange. Their scientists simply feel there isn't any evidence to link defoliation with human problems. But after researching this report and listening to the recommendations of the leading dioxin scientists in the country, we feel there is a need for immediate testing of all Vietnam veterans who handled Agent Orange or went into sprayed areas. Not only for the sake of those who have told us of their symptoms but for the countless others whose lives and whose children's lives could be blighted by the dioxin poison in Agent Orange" (Young, 1981a).

In this period, the US audience was ready to accept the responsibility of Agent Orange for, wrote Gough "the United States public long ago disenchanted with the Vietnam war and, by the late 1970s, immersed in guilt about its treatment of Vietnam veterans, willingly accepted the idea that a chemical mixture - Agent Orange - was at the root of veterans' complaints" (Gough, 2005). In this respect, during the 12 years that followed the documentary, the US Government, other government institutions and chemical companies conducted hundred of studies on populations, including veterans, potentially exposed to TCDD and phenoxy herbicides (Young, 2002). Local and national media reported on Agent Orange and veterans' complaints with more frequency" ([Anonymous], 1997; Meyers, 1979).

As regards the adverse effects of Agent Orange exposure on humans, the VA gave its position on October 11, 1978. Dr. Paul A. Haber - Assistant Chief Medical Director for Professional Services, Department of Medicine and Surgery, VA - stated that "the only human disorder which can definitely be linked to herbicide exposure is chloracne. The lesion may heal completely or result in scar tissue. Temporary symptoms can be produced after heavy exposure, including nausea, diarrhoea, fatigue, loss of appetite, headaches, backaches, cutaneous sensory deficiency, impaired olfactory or gustatory sensation and temporary local muscle paralysis. These symptoms disappear after a short period of time. Many statements regarding chronic adverse effects of herbicides in man are unsubstantiated at this time." Haber pointed out the significant difference between the number of veterans who have reported to VA medical centres for medical examination and the large number claimed in public media to have been exposed to, or to have become ill from, the effects of herbicides: "during the period 1962 through 1971 […] it was theoretically possible that 4.2 million American soldiers could have made transient or significant contact with the herbicides. […] By contrast no complaint referable to this use of herbicides reached the VA before 1978. By close of business on June 30, 1978, fewer than 300 veterans had presented themselves at VA medical centres for health problems they believed had been caused by exposure to the herbicides, although a large number had applied for veterans' benefits" ([Anonymous], 1978a).

The VA Compensation and Pension Service provided the US Air Force with data on the first 361 claims filed by veterans who alleged health alterations due to exposure to herbicides. Among these patients, 13 had alleged exposure only, without any symptoms. Skin diseases represented 48.9% of the alleged diseases, which included various other problems, notably: psychiatric [27.6%], ear, nose and throat [14.4%], cancer [13.8%] and peripheral neuropathy [12.1%]. Only 3 of the 361 claims mentioned chloracne and none of them could be confirmed by physical examination ([Anonymous], 1979).

In 1979, the White House established an "Interagency Work Group" to study the possible health effects of phenoxy herbicides, including the long-term effects. The group included staff from the Department of Health and Human Services [chair], the Department of Defense, the Department of Agriculture, the Department of Labour, the Congressional Office of Technology Assessment, the EPA, the VA and the White House Office of Science and Technology Policy.

The Work Group identified veterans who had been exposed and who were to be medically examinated and also endorsed follow-up studies on individuals in the private sector who had been occupationally or accidentally exposed to dioxin. Ten epidemiologic studies of Vietnam veterans and five health surveillance projects were initiated. It was concluded from these studies that chloracne may persist for 30 years after exposure to dioxin; there was no evidence to support a relationship between herbicide exposure and findings of adverse health effects in the Operation Ranch Hand group at the time of the examination. Concerning the possible consequences of dioxin exposure on reproduction, no paternally mediated effect was found (Reggiani, 1988b).

Another event drew attention to the claims of some Vietnam veterans that Agent orange could be responsible for diseases: “in the spring of 1978 a 28-yearold man, a self proclaimed “health nut”, appeared on the *Today Show* where he shocked many of the program’s viewers by announcing ‘I died in Vietnam but I didn’t even know it’. On December 14, 1978 [he] succumbed to the cancer that had destroyed much of his colon, stomach and abdomen. In the months before he died, Paul Reutershan had founded Agent Orange Victims International [AOVI] and spent all his waning energies trying to inform the American people about his belief that his cancer was the result of his exposure to Agent Orange” (Wilcox, 2011). Following his death in 1979, “AOVI brought on workman’s compensation attorney Victor Yannacone, who filed Reutershan’s complaint as a class action lawsuit against six of the chemical companies as defendants, Dow Chemical, Monsanto, Hercules, Northwest Industries, Diamond Shamrock and North American Phillips” ([Anonymous], 2010c).

The companies filed a third-party action against the US government and a similar class action was filed in July 1981 against the VA and the Department of Defense. Some 2.4 million Vietnam veterans including 1,200 from Operation Ranch Hand and 20 civilians involved in the destruction of of the Agent Orange surplus, were presumed to have been exposed. More than 1,250 lawyers from 150 American law firms were involved in the litigation. Monsanto denied its responsibility stating that “the available scientific and medical evidence does not support the claims alleged in the veterans lawsuits”. According to Monsanto, the evidence included: the report issued by the National Academy of Science in 1974 that concluded the absence of association between human health problems and exposure to Agent Orange; the “more than 40,000 scientific papers over 35 years that repeatedly concluded that the phenoxy herbicides are not significantly hazardous to humans; the statements by the VA and the EPA that they had not observed any long-term health hazard related to exposure to Agent Orange; a series of workshops sponsored by the American Farm Bureau that reported the absence of adverse effects on human reproduction after exposure to 2,4,5-T or TCDD ([Anonymous], 1980a).

In May 1984, the corporation defendants came to an out-of-court agreement: although they did not admit culpability they set aside $ 180 million for distribution to claimants ([Anonymous], 1984b). It was decided that $ 150 million would be designated for compensation to veterans who suffered total disability and the survivors of the veterans who had died. The compensation was paid

out by the companies in proportion to the amount of herbicides they produced. The settlement was invested in a fund that mailed its first checks to veterans in March 1989. Those who were rated 100% disabled received up to $ 12,800, paid out over 10 years. The fund closed in 1997, after it had distributed $ 197 million to about 52,000 American veterans and their families. The average payment was $ 3,800. The fund also distributed $ 74 million to social service programs ([Anonymous], 2010c). The maximum amount of money received by veterans totally disabled before January 1985 was $ 25,000 (Gough, 1987).

Further investigations. The "Ranch Hand" Program

In 1980, the American Medical Association's [AMA] Council on Scientific Affairs set up a programme to review the scientific information on Agent Orange. The AMA published its conclusions in October 1981, under the title "The health effects of Agent Orange and Polychlorinated Dioxin contaminants". An abridged version was published in the *Journal of the American Medical Association* on October 15, 1982 (Jones, 1982). Besides the veterans population, industrial workers were regarded as the most exposed, both during manufacture and sometimes when the process went out of control. The AMA recorded 579 workers exposed to TCDD since 1949 [Nitro plant] including 156 employees in the ICMESA plant at Seveso "one of the most extensive human experience with the adverse effects on TCDD in man." The panel in charge of the programme pointed that for the workers in the ICMESA plant, "except for the skin, no organ or body functions were impaired. No derangement of gestation, no foetal lethality and loss, no gross malformations, no growth retardation at term and cytogenetic abnormalities have yet occurred."

The Panel concluded quite prudently that "in spite of the voluminous data on the biological effects of the phenoxy-type pesticide and their associated chlorinated dioxins, there is still very little substantive evidence for the many claims that have been made against these compounds. The most serious of these allegations assert that Agent Orange or compounds of a like nature have caused malignant tumours, spontaneous abortions and birth defects. Although data from studies on experimental animals tend to support some of these claims, it is not certain that animal data are extrapolable to man. No laboratory animal can fully substitute for man; we must therefore depend on the results of on-going epidemiology on persons who are known to have been exposed." Regarding chloracne, the AMA stressed its value: "If there is no history of chloracne, then the likelihood of a significant exposure to or adverse health effects from TCDD is remote. Hence chloracne is the clinical marker of TCDD exposure."

The AMA's report was updated in 1984. Concerning the cancer studies, the AMA Panel asserted that "a causal relationship between STS and dioxin exposure has not yet been confirmed or excluded." It also reported a case-control study conducted in the Pacific Northwest that did not support a link between STS, Hodgkin's disease and non-Hodgkin lymphomas and exposure to phenoxy herbicides or chlorophenols. The Panel concluded that "the studies to date on the human

health effects of Vietnam exposure to Agent Orange do not reveal a clear relationship between serious illness and exposure." It stressed the value of chloracne as a "marker for biologically effective exposure in humans [that] may persist as long as 30 years."

Two years before the AMA programme in October 1978, the Air Force Deputy Surgeon General had made a commitment to Congress and the White House to conduct a health study on the Operation Ranch Hand population. The objectives of the Ranch Hand Program were to determine whether there were long-term effects from occupational exposure to Agent Orange and other herbicides during military service in Vietnam between 1962 and 1971. The matched cohort incorporated 1,188 Air Force "Ranch Hand" personnel involved in the spraying operations (Buckingham, 1983; Gunby, 1979). The cohort was compared to a group of veterans [1731] who served in Southeast Asia, not occupationally exposed to herbicides in Vietnam. Their population was of sufficient size and their training similar to that of the Ranch Handers. Physical examinations were performed in 1982, 1985, 1987, 1992, 1997 and 2002.

The first mortality report of the Ranch Hand Program published on June 30, 1983 did not show any unusual finding. Minor birth defects such as birth marks were observed in the Ranch Hand group. No significant differences were noted between the Ranch Hand and the control groups with respect to the occurrence of systemic cancers, blood abnormalities or cardiovascular, renal, pulmonary, hepatic and neurologic effects. No chloracne, porphyria cutanea tarda or STS was noted in the exposed individuals.

Commenting on the Ranch Hand report, the Panel of the AMA concluded "while it is premature to accept these findings as conclusive, they should be reassuring to Ranch Handers because no major clinical health problems have surfaced and the men are overall [in] good general health for [their] age." The Panel however underlined the necessity of follow-up examinations at 3, 5, 15 and 20 years.

The US Air Force's second mortality report released in February 1985 did not show any further significant differences in the number of deaths between the Ranch Hand and the comparison groups. However, as previously, the AMA Panel still pointed out that "it may still be too early to see the development of conditions that might be attributable to herbicide exposure" (Beljan *et al.*, 1984).

Regarding the possible veterans' risks for fathering babies with birth defects, an additional case-control study concluded that the data contained no evidence to support the fear that veterans had a greater risk than any other men (Erickson *et al.*, 1984). However, despite these reassuring conclusions, some abnormalities - higher incidence than normal of non melanoma skin cancer, birth marks and higher incidence of subjective psychological disorders - were regarded by the veterans groups as more alarming than the author's study, which was suspected of giving the Ranch Handers "a clean bill of health" (Fox, 1984).

In 1987, 995 Ranch Handers [i.e. 84% of the eligible cohort] and 1,299 veterans from the comparison group [i.e. 75%] attended the follow-up. The panel of physicians in charge of the

examination concluded that dermatological findings were similar in both groups. No cutaneous lesions compatible with chloracne diagnosis was seen. The immunological status of the groups, the hepatic tests and cardiovascular results were also similar. Only basal cell carcinomas were significantly more frequent in Ranch Handers. No significant difference was found between the groups for systemic cancers at any particular site. The panel of physicians underlined that the absence of chloracne in the Ranch Hand group during or since their TCDD exposure in Vietnam was consistent with the absence of chloracne-associated health effects. They concluded that there was insufficient evidence for a definite causal relationship between herbicide exposure and averse health effects in the Ranch Hand group (Wolfe *et al.*, 1990).

The International Agency for Research on Cancer (IARC) also pointed out that no association between STS and military service in Vietnam could be demonstrated in the published studies in this respect, despite potential exposure to the heavily TCDD-contaminated chlorophenoxy herbicides that were used ([Anonymous], 1987b). Similarly, in the historical cohort study conducted by the CDC - namely the Vietnam Experience Study [VES] – 9,324 Vietnam veterans were compared with 8,989 non-Vietnam Army veterans who served in Korea, Germany or the US during the Vietnam era. The total number of cancer deaths was insufficient to obtain a valid conclusion on specific cancer types. Circulatory system diseases were the only natural cause of death for which the mortality rate among Vietnam veterans differed from that among non-Vietnam veterans ([Anonymous], 1987a).

An additional report compared 1,261 Ranch Hand veterans to 1,910 Air Force veterans not exposed to herbicides. No significant difference could be found between the Ranch Hand group and the comparison population for all-cause cumulative mortality. The investigators however found a statistically significant increase in digestive system deaths among Ranch Handers that was not considered as suggestive of a herbicide adverse effect (Michalek *et al.*, 1990).

The 1991, Ranch Hand Program report did not mentioned any serious health effect from exposure to Agent Orange. The overall all-cause mortality experience of the Ranch Handers was not regarded as significantly different from that expected. Dermatologic endpoints were not significantly associated with dioxin concentrations. Serum dioxin levels were not significantly associated with the incidence of skin neoplasms except for an increase in basal cell carcinomas on sites other than the ear, face, head or neck. As for neurological disease, psychological disorders, liver disease, haematologic symptoms, pulmonary disease and renal health no evidence was found to indicate an association with dioxin levels. The cardiovascular findings failed to find any evidence linked to dioxin levels among non-diabetics. The survey reported a significantly increased risk of essential hypertension among the Ranch Handers in the high dioxin category. A significant association was noted between serum dioxin levels and decreased testicular size, between serum dioxin levels and increased IgA levels and between glucose intolerance and dioxin; however, the authors considered it as premature to infer that dioxin could directly cause diabetes. A significant association between dioxin levels, high density lipoprotein and cholesterol HDL was also noted.

Finally, the authors concluded that "the study has not demonstrated health effects which can be conclusively attributed to herbicides or dioxin exposure." They noted the existence of a consistent relationship between dioxin and body fat for which they proposed two hypotheses: either dioxin causes an increase in body fat or the level of body fat influences the dioxin decay rate (Roegner *et al.*, 1991; Wolfe *et al.*, 1991).

In the 1998 report of the Ranch Hand Program, 118 Ranch Hand deaths were observed, whereas 120 were expected in the comparison population. The study showed strong evidence of an adverse relation between dioxin and diabetes. The authors failed to find any evidence of a relation between dioxin body burden [concentration] and cancer in Ranch Hand veterans. Regarding immune function and hematologic abnormalities, the results confirmed those previously observed. The authors of the 1998 survey noted an increased risk of a probable peripheral neuropathy among the Ranch Hand veterans in the high exposure category (Michalek *et al.*, 2001).

The 2006 report of the Ranch Hand Program concluded the absence of significant elevation in risk for spontaneous abortion or stillbirth. No association was seen between paternal dioxin level and intrauterine growth retardation. No increase in cancer mortality was observed. No evidence of chloracne was found. The prevalence of cardiovascular diseases did not appear to be associated with dioxin exposure. There was no clear evidence of psychological disorders that could be related to herbicide exposure (Robinson *et al.*, 2006).

The same year [2006], Kang et al. published the results of a survey of the Army Chemical Corps members who were responsible for the spraying of herbicides around base camps and aerial spraying from helicopters in Vietnam. The level of exposure of these individuals was regarded as similar to those of the Ranch Handers. 2,872 Vietnam veterans and 2,737 non-Vietnam veterans were identified as potential study participants. Selected participants were involved in chemical operation duties between July 4, 1965 and March 28, 1973. Serum dioxin concentration was measured for 73% of Vietnam veterans and 65 % of non-Vietnam veterans. An unequal number of blood specimens [collected in 1999-2000] were analysed due to the cost of the laboratory test [$1,000 per specimen]. A health interview collected self-reported data on medical conditions diagnosed by medical doctors. 1,499 Vietnam veterans and 1,428 non-Vietnam veterans completed the interview. The authors observed significant associations between a history of spraying herbicide and self-reported, physician-diagnosed diabetes, heart disease, hypertension and chronic respiratory diseases. They pointed out that the association between diabetes and a history of spraying herbicides was consistent with data from the Ranch Hand study. The authors also measured the serum TCDD concentration in a sample of 795 Vietnam veterans and 102 non-Vietnam veteran controls. They showed that those veterans who reported spraying herbicides had a significantly higher serum dioxin level than those who never sprayed herbicides. Concerning the risk of cancers, the authors concluded that the risk of all cancers among veterans exposed to herbicides was increased but not statistically significant (Kang *et al.*, 2006).

The results obtained by the Ranch Hand Program were the object of criticism from politicians involved in veterans' matters. Opening the congress of the Subcommittee on National Security, Veterans Affairs and International Relations on March 15, 2000, Representative Christopher Shays reported that the Ranch Hand study "has failed to fulfil its promise as the pivotal longitudinal study of herbicide toxicity. Some concluded it never will. Others believe the research was designed to fail or manipulated to avoid controversial findings." Sanders, a member of the Committee of Government Reform, pointed out that "we are not quite convinced that even that those people, who were most exposed to Agent Orange have been fully studied. It is beyond my comprehension that with all the resources of the US government, we have not been able to track down those people who are most exposed and take an objective look at the health problems that they have suffered. […] Only about 7,500 veterans have received service-connected disability compensation from the US government" ([Anonymous], 2000a).

Additional veterans' claims. Further debates and controversies. Political interference

By October 1, 1983, 9,170 veterans filed claims for disabilities caused by exposure to Agent Orange. The VA refused compensation to 7,709 of them, considering that the alleged diseases were not service connected. Only chloracne was regarded as related to Agent Orange exposure (Zumwalt, 1990). As the majority of claimants could not obtain compensation, on October 24, 1984, the US Congress passed the "Veterans' Dioxin and Radiation Exposure Compensation Standards Act". Its purpose was "to ensure that VA disability compensation is provided to veterans who were exposed during service in the Armed Forces in the Republic of Vietnam to a herbicide containing dioxin […] on sound scientific and medical evidence to such service." As there was "some evidence that chloracne, porphyria cutanea tarda, and STS are associated with exposure to certain levels of dioxin as found in some herbicides", a Veterans' Advisory Committee and a Scientific Council were formed to make "findings and evaluations regarding pertinent scientific studies". Moreover, the Veterans' Dioxin and Radiation Exposure Compensation Standards Act pointed out that "it has always been the policy of VA and is the policy of the United States, with respect to individual claims for service connection of diseases and disabilities, that when, after consideration of all evidence and material of record, there is an approximate balance of positive and negative evidence regarding the merits of an issue material to the determination of a claim, the benefit of the doubt in resolving each such issue shall be given to the claimants" ([Anonymous], 1984c).

On October 6, 1989, Admiral Zumwalt, Commander, Naval Forces Vietnam from 1968 to 1970, was appointed as special assistant to the Secretary of the Department of the VA. Whereas previous official reports denied major effects of Agent Orange on veterans' health, Zumwalt proposed a different approach. He asked four reviewers to assess the validity of the work of the Advisory Committee of the NAS and published a report in 1990, the purpose of which was to point

out “political interference in government-sponsored studies associated with Agent Orange [that] has been the norm, not the exception. In fact it appeared that systematic efforts were made to suppress critical data or alter results to meet preconceived notions of what alleged scientific studies were meant to find”. Zumwalt asserted that “without exception, the experts who reviewed the works of the Advisory Committee disagreed with its findings and further questioned the validity of the Advisory Committee’s review of studies on non-Hodgkin lymphomas. He mentioned a “distinguish group at the Fred Hutchinson Cancer Research Institute in Seattle, Washington” who considered that it is at least as likely as not that there is a significant association [as defined by the Secretary of the VA] between exposure to phenoxy herbicides and non-Hodgkin lymphoma”. The same group, wrote Zumwalt, regarded the Committee’s work as “not sensible” and “rather unsatisfactory”. Zumwalt also quoted Hartzman “one of the US Navy’s top medical researchers” who attested that “an inadequate process is being used to evaluate scientific publications for use in public policy”. Stellman and Stellman who composed the third team of reviewers stated that cancer studies relevant to herbicide exposure presented “a stunning indictment of the Advisory Committee’s scientific interpretation and policy judgments regarding the link between Agent Orange and Vietnam veterans.” The fourth reviewer, the name of whom is not provided by Zumwalt, shared the conclusions of the others and considered the work of the Committee “has little or no scientific merit and should not serve as a basis for compensation or regulatory decisions of any sort.”

Regarding the CDC’s works commissioned by the Congress, Zumwalt considered the conclusions “were so ill conceived as to suggest that political pressures once again interfered with the kind of professional, unbiased review the Congress had sought to obtain.” As regards the Ranch Hand study, Zumwalt quoted the statement of Senator Daschle who “disclosed compelling evidence of additional political interference with the Air Force Ranch Hand Study.” He also denounced the behaviour of Dow Chemical that, he wrote, was aware as early as 1964 that TCDD was a contaminant of the manufacturing process of Agent Orange. According to him, this was additional evidence of the “efforts of government and industry to obscure the serious health consequences of exposure to dioxin.”

Zumwalt concluded that almost all diseases, notably cancers, alleged by the Vietnam veterans might be caused by Agent Orange: “there is adequate evidence for the Secretary to reasonably conclude that it is at least as likely as not that there is a relationship between exposure to Agent Orange and the following health problems: non-Hodgkin lymphoma, chloracne and other skin disorders, lip cancer, bone cancer, STS, birth defects, skin cancer, porphyria cutanea tarda and other liver disorders, Hodgkin’s disease, haematopoietic diseases, multiple myeloma, neurological defects, autoimmune diseases and disorders, leukaemia, lung cancer, kidney cancer, malignant melanoma, pancreatic cancer, stomach cancer, colon cancer, nasal/pharyngeal/oesophageal cancers, prostate cancer, testicular cancer, liver cancer, brain cancer, psychological effects and gastro intestinal diseases. […] it is evident to me that enough is known about the current trends in the

study of dioxins and their linkage with certain cancers upon exposure, to give the exposed Vietnam veterans the benefit of the doubt" (Zumwalt, 1990).

In January 1983, Zumwalt's eldest son, Elmo Zumwalt III, who served as a lieutenant during the Vietnam War was diagnosed with lymphoma. In 1985, it was discovered that he also had Hodgkin's disease. In addition, his grandson Elmo Russell Zumwalt IV had been born in 1977 with severe learning disabilities. Admiral Zumwalt and his family were then convinced that both son and grandson were victims of Agent Orange, which the Admiral had ordered to be sprayed over the Mekong Delta. In an article published in *The New York Times* in 1986, Elmo Zumwalt III said: "I am a lawyer and I don't think I could prove in court, by the weight of the existing scientific evidence, that Agent Orange is the cause of all the medical problems - nervous disorders, cancer and skin problems - reported by Vietnam veterans, or of their children's severe birth defects. But I am convinced that it is" ([Anonymous], 1988a).

The 1990 report prepared by the "Agent Orange Scientific Task Force" working with the American Legion, Vietnam Veterans of America, and the National Veterans Legal Services Project also concluded there was a significant statistical association between exposure to Agent Orange and non-Hodgkin lymphoma, STS, skin disorders/chloracne, subclinical hepatotoxic effects and porphyria cutanea tarda. The report indicated that the scientific evidence of a significant statistical association with exposure to Agent Orange is at least as strong as the evidence of a lack of the association for the following effects: Hodgkin's disease, neurologic effects, and reproductive and developmental effects ([Anonymous], 1990c).

Finally, in the early 1990s, although "thousands of scientific studies had been conducted, numerous government hearings had been held and veterans had pressed for conclusive answers", the question of the health effects of herbicides remained "shrouded in controversy and mistrust". In this context, the Office of Technology Assessment recommended that the Department of Veterans Affairs should call upon a panel of scientists with recognized expertise in understanding the health effects of exposure to dioxin. Congress therefore directed the Secretary of the VA by Public Law 102-4 - "the Agent Orange Act of 1991"- to establish a committee of the NAS to give advice on the health effects of Agent Orange. The Committee of the NAS had to "review and summarize the scientific evidence, and assess the strength thereof, concerning the association between exposure to a herbicide used in support of the United States and allied military operations in the Republic of Vietnam during the Vietnam era and each disease suspected to be associated with such exposure."

Regarding the "presumptions for service connections for diseases associated with exposure to certain herbicide agents", the Agent Orange Act of 1991 listed the diseases that "shall be considered to have been incurred in or aggravated by such service notwithstanding that there is no record of evidence of such disease during the period of such service. The diseases […] are the following: non-Hodgkin lymphoma becoming manifest to a degree of disability of 10% or more; each STS becoming manifest to a degree of disability of 10% or more other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma or mesothelioma; chloracne or another acneiform disease

consistent with chloracne becoming manifest to a degree of disability of 10% or more within one year after the last date on which the veteran performed active military, naval, or air service in the Republic of Vietnam during the Vietnam era. […] Any veteran who served in Vietnam between January 9, 1962, and May 7, 1975, and has one or more of the diseases on the list of presumptive conditions that the VA maintains, must be presumed by the VA to have been exposed to herbicides, and therefore that his or her disease is service-connected" ([Anonymous], 1991).

In February 1992, the Institute of Medicine [IOM] of the NAS signed an agreement with the Department of the VA "to review and summarize the strength of the scientific evidence concerning the association between herbicide exposure during Vietnam service and each disease or condition suspected to be associated with such exposure." After reviewing the scientific literature, the Committee realized that the epidemiologic database was actually lacking in quantitative measures of individual exposure to herbicides, a "key component in determining whether specific health outcomes are associated with exposure to dioxin". Despite the absence of such data, the Committee concluded that "Vietnam veterans as a group had substantially lower exposure to herbicides and dioxin than the subjects in many occupational studies". The Ranch Handers were however regarded as exceptions.

The diseases were classified into four categories according to the strength of evidence that linked health effects with herbicide exposure. The Committee found sufficient evidence for a positive association with herbicide and/or TCDD only with STS, Hodgkin's disease, and non-Hodgkin lymphoma. Besides these malignant diseases, the Committee found evidence for an association with two other diseases: chloracne and porphyria cutanea tarda. The second classification involved diseases in which "limited or suggestive evidence" suggested such an association, i.e. at least one high-quality epidemiologic study has found a link but that the evidence is not conclusive enough to rule out chance or study bias influencing the results. The other two categories involved conditions for which there is "inadequate or insufficient evidence" to determine the existence of a link or "limited or suggestive evidence of no association". The report of the NAS IOM's Committee published for the first time in 1994 was updated biannually ([Anonymous], 1994).

In 1998, porphyria cutanea tarda was deleted from this group of diseases and integrated into the group of diseases for which only limited or suggestive evidence exists. Chronic lymphocytic leukaemia was added in 2002. The Committee for Update 2008 suggested it was possible that epigenetic changes caused by herbicide exposure might be responsible for adverse effects in offspring. The Update 2012 did not confirm this concern and noted that "there is inadequate or insufficient evidence to determine whether there is an association between parental exposure to the chemicals of interest and birth defects other than spina bifida, childhood cancers or disease in their children as they mature or in later generations" ([Anonymous], 2014b).

Frumkin pointed out that the studies conducted in a dozen states, mostly in the Midwest and Northeast [including New York, Wisconsin, Massachusetts and Michigan] and the studies on

Australian Vietnam veterans were also limited by their small sample sizes, by the absence of detailed exposure assessment and by the relatively young age of the soldiers involved. Due to the insufficient results that could be obtained from the studies of Vietnam veterans, indirect sources of information were used: civilians and Vietnamese soldiers exposed to the same herbicides as US veterans, herbicide manufacturing workers, farmers and all workers occupationally or accidentally exposed to dioxins in the US and Europe. Frumkin concluded that: studies of Vietnam veterans have not demonstrated an increase in STS, notably no association was shown in the Ranch Hand study; most studies of Vietnam veterans have neither demonstrated an increase in non-Hodgkin lymphoma nor an increase in Hodgkin's disease; no significant association with gastrointestinal cancers or brain cancer was documented; the Australian Veteran Study showed an excess of prostate cancer whereas the Ranch Hand study failed to find such a link; as regards multiple myeloma, no study of Vietnam veterans was informative due to the small number of cases; three studies have pointed to an association between paternal Agent Orange exposure and acute myeloid leukaemia (Frumkin, 2003).

In 2003, the Veterans Benefits Acts directed the Secretary of Veterans to contract with the NAS. Although the Committee of the NAS regarded the Air Force Health Study [AFHS] data assets as unique - "no other epidemiologic dataset on Vietnam veterans contains as detailed information over as long a time period" - it pointed out "several weaknesses that limit its utility as a means of evaluation of the health impact of Agent Orange exposure. These include the inherently small size of the cohort, the fact that the cohort is unrepresentative of intheater veterans, lack of any biomarkers of herbicide exposure other than TCDD, little information on subjects' locations in the theatre of operations, unavailability of detailed exposure history and possible herbicide exposure of? the comparison group." In this context, the Committee of the NAS proposed an independent oversight of the AFSH data assets conducted by "8-12 established scientists representing a range of appropriate disciplines. […] Two lay members […] should be included to provide insights from the participant and veterans perspective." *Roughly speaking* [sic] "the Committee estimates that $150,000 to $300,000 per year would be required […] and an additional $200,000 or more per year for proper maintenance of the biospecimens." The Committee of the NAS considered however that "the costs of properly documenting the data assets, making them available to the research community, and implementing the proposed 5-year program to encourage their use are small in comparison with the government's investment of $143 million to date" ([Anonymous], 2006).

Focusing on chloracne and skin diseases

Using the data from ten years of follow-up in the Air Force Health Study, Burton et al. determined cumulative prevalence of skin diseases mentioned in the physical examinations performed on the Ranch Hand veterans in 1982, 1985, 1987 and 1992. The patients were examined by dermatologists who had been trained to become familiar with the clinical features of chloracne. The diagnosis of skin diseases was based on these examinations or on the review of medical records

after self-reporting during the interviews conducted during each physical examination. No case of chloracne was found at any of the clinical examinations and no case was reported in the review of the medical records. The reading of the medical records revealed only one case, in October 1967, of pruritus on arms and feet later involving the forehead. The authors concluded that either the exposure received by the Ranch Handers was not sufficient to cause chloracne or that chloracne happened but had resolved and became undetectable by the time of the examinations. The former interpretation was supported by the low dioxin levels compared to the dioxin levels of those in Seveso who experienced chloracne (Burton *et al.*, 1998). By contrast, Fleck published the self-reported case of chloracne that affected a Vietnam veteran exposed to Agent Orange from 1966 to 1967, who experienced skin contact and ingestion of contaminated food and water. The man related the appearance of chloracne on exposed shoulders, arms and buttocks, without any medical confirmation. He also mentioned neurological symptoms including numbness, paraesthesias and fasciculations (Fleck, 1985).

The Vietnam veterans' health status was assessed by the CDC from a sample of enlisted men who entered the US Army from 1965 through 1971. 7,924 Vietnam and 7,364 non-Vietnam veterans participated in a telephone interview; a subsample of 2,490 Vietnam and 1,972 non-Vietnam veterans also underwent extensive physical and psychological health examination by board-certified physicians. Only a few differences were found between both groups: hearing loss, stool occult blood, and evidence of past hepatitis B were the most noteworthy. When semen samples were examined, the study showed a decrease in the Vietnam veterans' sperm concentrations and a decrease in the average proportion of normal sperm cells. Vietnam and non-Vietnam veterans however fathered a similar number of children ([Anonymous], 1988b). Although Vietnam veterans more frequently reported chloracne than non-Vietnam veterans it was not confirmed by physical examination [1.9% vs 0.3%]. Chloracne-like lesions, hirsutism and skin cancers were rare and occurred with similar frequency in both cohorts ([Anonymous], 1989).

In the retrospective chart review for 100 patients enrolled in the Agent Orange Exposure Registry between January 2009 and May 2010, Clemens et al. numbered 43% with chloracne. The authors also investigated the relationship between skin cancers and Agent Orange exposure. Fifty-one percent of patients had non-melanotic invasive skin cancer; the incidence rate was found significantly higher than that of the general population of similar age. The incidence was significantly higher among patients who actively sprayed TCDD-containing mixtures than among those patients who worked or lived in a contaminated area and also higher among patients with chloracne than those who did not experience chloracne. The mean time between exposure and the first non-melanotic skin cancer diagnosis was 28 years. The incidence of cutaneous melanoma was 10% whereas the overall incidence of melanoma was 3.8% in the US general population. Besides these cutaneous cancers, 26% had various malignancies including prostate, bladder, laryngeal, colon, lung and testicular cancers, leukaemia and myeloma (Clemens *et al.*, 2014; Sorg, 2015a).

Finally, regarding chloracne in chemical warfare, only Plewig published quite impressive pictures of a male Iranian patient who served as a soldier in the Iran-Irak war in the 1980s. The patient was covered with chloracne lesions [Plewig called it Halowax acne]. Although the source was not identified, the patient reported gas exposure (Plewig and Kligman, 2000). He also reported that several of his friends were affected by the same disease. The authors could not examine them (Plewig, 2015).

Evaluation of the health effects of Agent Orange: a "conflict between science and social concerns" (Young, 2008)

Hammond and Schecter underlined how scientifically controversial, politically charged and misunderstood Agent Orange and its effects are. In this context, they added, filtering through what is fact and what is fiction is extremely challenging (Hammond and Schecter, 2012). Meyers also pointed out how the responsibility of Agent Orange in the occurrence of adverse health effects illustrates the "fascinating interplay of diverse elements of [the US] political fabric involving the NAS, the National Cancer Institute, the National Institute of Health, the American Association for the Advancement of Science, a spate of independent scientists, a host of executive departments and agencies, the departments of Defense, Agriculture, Interior and HEW [Health, Education and Welfare], the Air Force, the Surgeon General, the State Department, the Office of the President and the Congress" (Meyers, 1979).

Young, who authored several publications on Agent Orange, pointed out that one of the main questions that has to be considered is "why is the Agent Orange surfacing ten years after it was used in Vietnam ?" He suggested two answers: either the presumed health effects have just appeared and have been diagnosed ten years after the exposure or the general public and Congress have eventually recognized the concerns of Vietnam veterans tht were initially denied.

In fact, due to the anti-war sentiment that pervaded the last years of the conflict, when the veterans came back home, many Americans refused to acknowledge their patriotic effort ([Anonymous], 1994) and even regarded them as "baby killers" (Gough, 1987).

Young et al. also underlined the role played by the media in these social and scientific interferences. To illustrate this matter, they quoted an article issued in 1974 in a Russian scientific paper according to which in the period from 1961 to 1969, 1,293,000 persons of the Provisional Revolutionary Government of the Republic of South Vietnam were subjected to the effects of poisonous chemicals. The same paper alleged that in the first ten months of 1970, 185,000 cases of persons being poisoned were recorded and 300 of them died (Young *et al.*, 1978). Decouflé et al. also stressed the influence of the media on the self-perceived health status of veterans. In telephone interviews conducted with more than 15,000 men who served during the Vietnam era, the authors found a strong positive association between numerous reported health outcomes and self-reported herbicide exposure. Decouflé et al. regarded the association as a likely result of a combination of

psychological stress reactions and conditioning by intense media portrayal of herbicides as a health threat that produced somatization and increased medical care (Decoufle *et al.*, 1992). Young et al., (all of them US Air Force officers, also pointed out that in the episodes where TCDD was confirmed as the causative agent, no human death was reported. In this respect, they regarded the scientific literature about these episodes as "the result of emotionalism associated with zealous press coverage" (Young, 1981b). Patterson et al. underlined the contrast between the higher incidence of chloracne and various skin diseases self-reported by veterans and dermatologic examination of the patients that did not confirm these self-reported skin diseases. They suggested that the increased rates of psychiatric comorbidities may act as a potential psychogenic component to health issues encountered following Vietnam service (Patterson *et al.*, 2016).

In fact, Young pointed out that the studies on Agent Orange have provided ample evidence that most veterans [and Vietnamese] were not exposed. A study conducted by the CDC on 646 ground combat troops who served in exposed units compared to 97 non-Vietnam veterans, showed they had no elevated blood levels of TCDD. Moreover, the blood TCDD levels of the exposed troops were not related to the estimate of Agent Orange exposure derived from military records or self-reported ([Anonymous], 1988d). An additional study published three years later led to the same conclusions: the adipose tissue concentration of dioxin in 36 Vietnam veterans was not significantly different from the concentration found in 79 non-Vietnam veterans and 80 non-veterans. The authors finally suggested that heavy exposure to Agent Orange or dioxin for most US troops was unlikely (Kang *et al.*, 1991).

Gough also underlined several points that questioned the value of the official conclusions with regard to the health effects of Agent Orange exposure. He expressed severe criticism of the quality of the literature the members of the IOM Committee examined. According to him, "a glance at the reference lists at the end of each chapter in the IOM 1994 report reveals [that] some of those papers are good, some bad, and some criminally bad." Moreover, wrote Gough, many committee members had conflicts of interest. Finally, "the IOM committees have not provided scientific advice to Congress […] it has picked and chosen data." Gough concluded that "when government, either Congress and its agent the IOM, in the case of Agent Orange, or the Executive Branch, through EPA, in the case of dioxin, decides that a risk exists, it […] hires additional people to work on the risk. Year after year those people produce more and more documents. With the passage of time, organizations that might oppose the government drop out because of expense or because they move on to other things. Few people remain to dissent, to say the risk is exaggerated or, even, non existent." In this context, the scientific arguments that did not support the conclusions of the media had to face a barrier: "science will lose - even when "science points in the direction of no elevated exposure to dioxin in Vietnam veterans - and society will pay the price in misplaced priorities and decisions" (Gough, 1991). Gough doubted that anyone besides the Air Force investigators who were under enormous political pressure to find something associated with Agent Orange, an IOM committee and some champions of Vietnam veterans' health claims, would interpret the available

data to indicate that any connection exists. Incidentally, according to Gough, about $3 billion had been spent on researching possible health effects from dioxin (Gough, 2005).

Stellman and Stellman actually underlined that the most difficult problems with regard to the adverse effects of Agent Orange among veterans was to define which troops were exposed and the extent of exposure: “only by determining concentrations in each study subject and only by attaching significance to ‘elevated levels’ that are commonly found in non-occupationally exposed people who never served in Vietnam, would it be possible to identify exposed veterans” (Stellman and Stellman, 1986). However, the serum dioxin test, regarded as the gold standard for this chemical exposure, due to its high cost, could be used in a limited number of studies (Stellman *et al.*, 2003).

Finally, the decision of the Congress [Agent Orange Act of 1991] would have been a response to veterans’ claims by directing the VA to pay compensation “basing its decision on compassion.” The determination of whether a disease was service.connected was not based on proof of exposure but on whether the evidence as judged by the NAS was sufficient to conclude that there was a positive association (Young, 2002). Moreover, the increased respectability gained by veterans in the years that followed the Vietnam war coincided with American interest in environmental questions and would reflect contemporary fears that chemical compounds could provoke a widespread sensitivity crisis (Jones, 2006). In this respect, Young wrote “the action by the United States Congress via the Agent Orange Act of 1991 provided presumptive compensation, an expression by the political system that was intended to acknowledge the sacrifices of the Vietnam veterans. Unfortunately, it has not met its objective. Few veterans have been compensated and litigation has once again become the hallmark of today’s action on Agent Orange and dioxin” (Young, 2008).

The US Department of the VA established rate tables on disability compensation and how much the VA pays ([Anonymous], 2016b). The *Agent Orange Review* informed veterans that “the disability must have been incurred or aggravated during active military service. [….] Disability compensation varies according to the degree of disability and the number of dependents. Benefits are not subjects to Federal or state income tax. […] The disability ratings range from 0 to 100 %. For example in 2004, a veteran with a disability rating of 10% receives $ 106; a veteran with a disability rating of 50% gets $646; and a veteran who is totally disabled and evaluated at 100 % receives $ 2,239 monthly” ([Anonymous], 2004c). At the end of 2001, the VA was compensating 9,000 Vietnam veterans.

The “almost forgotten” Vietnamese population

On May 9 1979, Tung who had become Vice Minister for Health in North Vietnam visited the US to promote scientific exchange and cooperation. He proposed that Vietnam and the US cooperate on a study on dioxin and its health effects. Allen, a toxicologist of the University of Wisconsin, replied that “our first obligation is to do a thorough study of our veterans who are also

an easier group to study than the Vietnamese population" (Wade, 1979). In fact, apart from the publications - the methodology of which was questioned - written by Tung et al. between 1973 and 1978 [see above] and Phuong et al. who pointed out possible congenital abnormalities, no study had considered the effects of Agent Orange herbicides on the Vietnamese population (Phuong *et al.*, 1989). Hay also quoted the works of Vietnamese cytologists published in Vietnam, who claimed that the incidence of chromosome damage in people exposed to 2,4,5-T was higher than expected. They, however, admitted that the number of cases was too small to be statistically significant (Hay, 1978).

After the foundation by the Vietnamese government in October 1980 of the 10-80 Committee (named after the date of its establishment) for the investigation of the consequences of Agent Orange and other chemicals, an international symposium on Herbicides and Defoliants in War was held in Ho Chi Minh City, from 13 to 20 January 1983, attended by 160 scientists from 21 countries. Chloracne was not considered as a major clinical adverse effect among the Vietnamese. The participants hypothesized that this might be related to the amount of fat in the skin or genotypic differences between the US and Vietnamese populations. The attendees drew attentiont to an increase in miscarriages, stillbirths and birth defects among the South Vietnamese veterans and exposed females. A similar increase was reported among North Vietnamese women married to exposed North Vietnamese veterans (Carlson, 1983). Two reports from South Vietnam studied the differences in the rate of occurrence of congenital abnormalities between the children of mothers who had been sprayed with herbicides and those who had not. Although these works suggested adverse effects of dioxin, it was agreed that the results were not conclusive and needed more statistical and methodological refinement (Constable, 1983). Due to the persistence of TCDD in human tissue [see appendix V], the potential effects of herbicides however remained of great concern to the Vietnamese people, 80% of whom lived in rural zones, wore open sandals or walked barefoot, ate food grown on contaminated soils and drank water from contaminated areas.

Moreover, Schecter et al. underscored the interest in understanding the health effects of dioxin exposure not only for the "almost forgotten Vietnamese" but also for the one million immigrants from Laos, Vietnam and Cambodia living in the US. They conducted studies on milk collected in 1970 and 1973 from nursing mothers living in areas sprayed with Agent Orange and in control mothers living in unsprayed areas. In milk samples collected in 1970, the authors measured the highest dioxin levels reported to date, i.e. 1,832ppt TCDD. Three years later [the spraying of herbicides had ended in 1971] high levels of dioxin were still found in milk samples. Up to 103ppt were found in adipose tissue in the 1980s and pooled blood collected in 1991 and 1992 from southern Vietnam showed elevated dioxin levels. However, in northern Vietnam, where no Agent Orange was sprayed, the TCDD levels were below 2.9ppt. In 1995, dioxin levels were found to be similar to those observed in industrial countries (Schecter *et al.*, 1995).

More recently, Scialli et al reviewed the data published on TCDD in milk from Vietnamese women. The data showed that TCDD from breast feeding did not persist in a child past adolescence.

Their observations suggested that current TCDD concentrations in human milk in Vietnam are not elevated by Agent Orange used during the war. They also showed that the adult body burdens of TCDD are similar between individuals who were breast-fed and bottle-fed. They concluded that breastfeeding is not a mechanism by which TCDD from Agent Orange can be transmitted from one generation to the next (Scialli *et al.*, 2015).

Although the Vietnam Association of Victims of Agent Orange (VAVA) estimated that 2.1 to 4.8 million Vietnamese were exposed to Agent Orange during the war (Martin, 2012), Hammond and Schecter pointed out that the amount of disease caused by Agent Orange to Vietnamese and Vietnam veterans may never be fully characterized, notably because of the complexity and cost of valuable epidemiological studies. UNICEF-Vietnam estimated that about 1.2 million children had some disability, although Hammond and Schecter concluded it was impossible to link the children's disabilities with a parental exposure to dioxin. Moreover, the cost of a dioxin blood analysis that could determine whether a parent had high dioxin exposure would be about $1,000 and would not prove a definite relationship between birth defects and dioxin exposure. In this respect, wrote the authors, it was the lack of evidence between birth defects and exposure to dioxin that caused a long stalemate between the US and Vietnamese governments, until 2000 when both governments set up a joint research program on herbicide health effects. (Hammond and Schecter, 2012).

After President Clinton's visit in 2000, the US and Vietnam signed, in March 2002, a memorandum of understanding that specified future collaborative research on the adverse effects of dioxin on health and the environment. A few years later, the Bush administration was reluctant to provide assistance to Vietnamese people affected with health problems related to dioxin exposure.

In 2004, the VAVA filed a class action lawsuit against Dow Chemical Co, Monsanto and 35 other chemical manufacturers, for war crimes. The suit used the Alien Tort Claims Act and alleged that the companies were in "violation of international laws and crimes and under the common law for product liability, negligent and intentional torts, civil conspiracy, public nuisance and unjust enrichment, seeking many damages for personal injuries, wrongful death and birth defects and seeking injunctive relief for environmental contamination and disgorgement of profits." The same judge who presided over the settlement between US veterans and the chemical manufacturer in 1984 [Jack Weinstein] ruled that the US took no part in any international agreement banning the use of herbicides during the time they were used in Vietnam. Consequently, herbicide manufacturers could not be considered as liable for personal injury. Moreover, the judge defined poison as "a substance that through its chemical action kills, injures or impairs an animal or organism". In this respect, as US military and manufacturers intended only to kill plants, Agent Orange could not be considered as a poison for human health (Edmoundson, 2012). On March 10, 2005, Judge Weinstein dismissed the lawsuit filed by the Vietnamese Victims of Agent Orange ([Anonymous], 2005). On February 22, 2008, the Federal Court of Appeal in Manhattan, NY, denied the Vietnamese plaintiffs' request to reinstate the lawsuit against the chemical companies that produced the herbicides ([Anonymous], 2010c). A year later, on February 27, 2009, the Supreme Court denied

the petitions made by the lawyers of the Vietnamese plaintiffs and by the lawyers of US veterans ([Anonymous], 2010c).

Finally, the Vietnamese authorities identified the victims as those people suffering with the following diseases: STS, non-Hodgkin lymphoma, Hodgkin's disease, chloracne, porphyria cutanea tarda, respiratory cancer, prostate cancer, multiple myeloma, spina bifida, peripheral neuropathy, type 2 diabetes, liver cancer, neurological defects, children with birth defects and reproductive abnormalities. Those who suffered from these conditions were eligible to receive compensation. In 2009, 200,000 of them were registered and received a monthly allowance of $ 17 ([Anonymous], 2009).

Recently, in France an additional lawsuit was filed against dioxin industrial manufacturers (Valo, 2021).

Chloracne, dioxin and politics: the Yushchenko case

Since Herxheimer's seminal description, chloracne had been observed in various circumstances including industrial exposures, both occupational or accidental, food ingestion, chemical warfare or as a consequence of environmental pollution. The Yushchenko case opened a new era in the history of dioxin and chloracne. For the first time, dioxin was used as a weapon intentionally administered to damage a single person. Due to the personality of the victim, a politician competing for the Ukraine presidency, the interference with political circumstances and the suspicion of criminal intention, the Yushchenko case was reported by news media worldwide. Besides this spectacular aspect, the case provided a unique opportunity for an in-depth investigation of an extreme phenotype of chloracne and finally for a better knowledge of the relationship between skin and dioxin.

Political background

In 1991, following the disintegration of the USSR, Ukraine became independent. Its first President, Leonid Kravchuk tried to assert the sovereignty of his country in breaking the former ties with its Russian neighbour. However, Ukraine was divided geographically, with a majority of people living in the eastern part of the country, including a minority of ethnic Russians close to the ex-USSR, and those living in the western part who favoured links with Europe. In this context, Kravchuk was defeated in the 1994 elections by Leonid Kuchma who proposed restoring the previous links with Russia. Re-elected president in 1999, Kuchma was identified, in 2000, on a recording recommending the killing of an investigative journalist - named Georgiy Gongadze - who had accused Kuchma of corruption.

After Gongadze's headless body was discovered, in November 2000, a few miles from Kiev, the population took to the streets and a movement named *Ukraine Without Kuchma* was created, led by Yulia Tymoshenko - who became Prime Minister in 2005. Kuchma became more and more unpopular to such an extent that in 2001 the *Ukraine Without Kuchma* movement demanded his resignation. Among the 25 candidates for the Ukraine presidency in 2004, two were the major characters: Viktor Yushchenko and Viktor Yanukovych.

Born 1950, in Donetsk province, Yanukovych was Vice-Governor and head of the provincial council of Donetsk between 1996 and 2001. He was named Prime Minister in 2002, by Kuchma. Convicted of robbery in 1967 and assault in 1970 and imprisoned for five years, Yanukovych favoured close links between Ukraine and Russia and, notably, advocated making Russian the official language of Ukraine.

Viktor Andriyovych Yushchenko born on February 23, 1954, graduated from the Ternopil Finance and Economics Institute in 1975 and, in 1993, was appointed Governor of the National

Bank of Ukraine. From 1999 till 2001, he was Prime Minister then went into opposition to President Kuchma and founded the *"Our Ukraine"* party [*Nasha Ukrayina*] which, at the 2002 parliamentary election, became Ukraine's most popular political force. Yushchenko advocated a combination of Ukrainian nationalism with ties to the European Union and membership of the North Atlantic Treaty Organization [NATO] (McKee, 2009).

Timeline of a medical and detective story

The Yushchenko dioxin story began when he "appeared for a hushed meeting an hour before midnight on Sunday September 5 2004, arriving in a black Mercedes-Benz at an exclusive dacha outside the capital". He was accompanied by a campaign manager. He had left his bodyguards behind. Waiting for the candidate were two leaders of the Security Service of Ukraine, or SBU, the country's successor to the KGB, including General Ihor P. Smeshko, its chairman. Mr. Yushchenko was leading in the presidential race. He had sought the meeting to discuss, among other things, death threats against him. The four men drank beer and ate boiled crayfish from a common bowl, as well as a salad made of tomatoes, cucumbers and corn. Later, they selected vodka and meats, and then cognac for a last drink. When the meeting ended about 2am, Mr. Yushchenko went home to bed and began to die, his supporters said. More than three months later, the dinner at the dacha has assumed the character of an Agatha Christie mystery mixed with a cold war spy tale. Mr. Yushchenko, his doctors said, had been poisoned. But how? And by whom?" (Chivers, 2004).

Due to the fact that food poisoning was rapidly suspected, the papers reported the menu that included at least one creamy dairy product - a dish of fermented mare's milk called "koumiss" - as well as sushi, crayfish, rye bread, watermelon, sweet cakes, wine, cognac and home-distilled vodka (Synovitz, 2004).

After Yushchenko had dinner, a severe headache and nausea developped . His wife reported the continuation of the story to Ukraine's newspaper *Zerkalo Nedeli*: "Viktor came home very late. I kissed him as usual and tasted something medical on my lips. I asked my husband, if he had taken medication. Viktor answered that he had not; he said he was tired." The following day [September 6] the symptoms worsened.

In an interview for *The Times* [London] on September 8, Yushchenko's doctor Nikolai Korpan claimed for the first time that the illness was the result of a deliberate attempt on the presidential candidate's life. Two days later, on September 10, Yushchenko was hospitalised at the Rudolfinerhaus Clinic in Vienna where he remained until September 18. He was diagnosed with acute pancreatitis, associated with ulcerations of the intestine and enlargement of the liver. According to Michael Zimpfer, President of the Rudolfinerhaus, Yushchenko was "severely ill and unable to walk, after five days of terrible abdominal pain. Initial testing showed that he had a high white-cell count and elevated liver and pancreas enzymes. His tests were negative for all the obvious possibilities, like hepatitis caused by a virus. Scans showed that his liver, pancreas and

intestine were, indeed, swollen. Internal examinations of the intestine using an endoscope found he had ulcerations - essentially bleeding abrasions - of the stomach and throughout his intestine and bowel as well. […] Already, doctors noticed that he was developing odd lesions on his face and trunk. […] He was severely ill, but this does not all add up to a single disease or even a known syndrome", Zimpfer said. The back pain was so intense that morphine had to be administered through an epidural catheter.

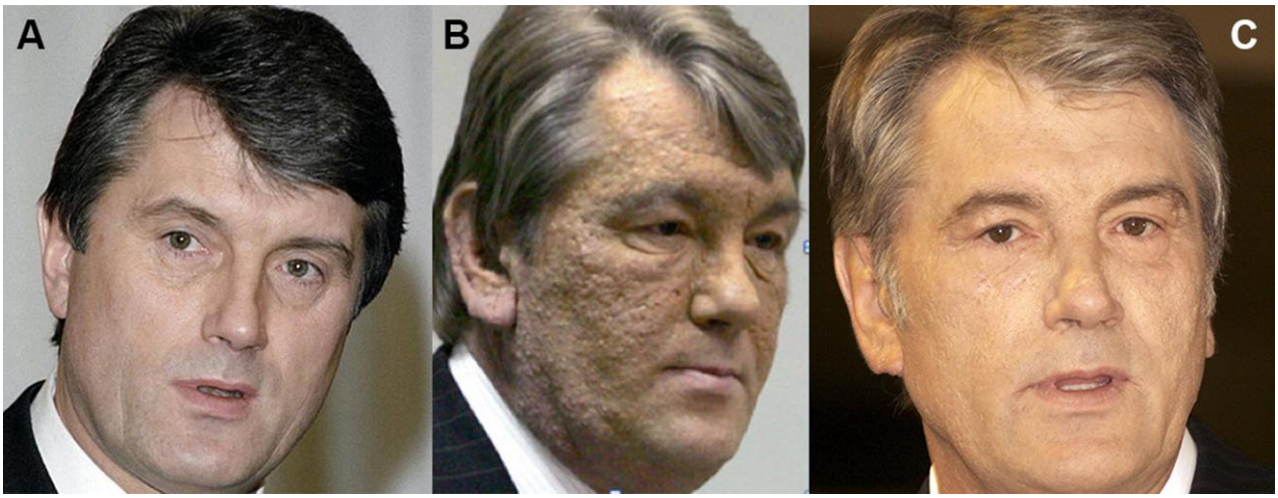


Figure 13. Victor Yushchenko poisoned by dioxin. A. Before poisoning. B. Three months after poisoning. C. Five years after poisoning. (From O.Sorg et al Lancet 2009)

In late September, Yushchenko previously a handsome candidate for the Ukraine presidency, appeared on TV channels and newspapers disfigured. His face was swollen and was a grey/green colour. It was covered with small nodules involving the retroauricular folds and ears, which rapidly transformed into inflamed and painful cysts. The periocular area was spared; nerve paralysis occurred on the left side of the face, with a discharge of tears and a bloodshot left eye (Ryan, 2005). In the following weeks, the skin lesions progressively covered up to 40% of the body (Figure 13).

Yushchenko, however, carried on his presidential campaign and spoke to the Ukrainian Parliament on September 21. "I am fortunate to be in this chamber today and will not take too much time but let me comment on some matter concerning each of you. During the last two weeks a number of Ukrainian politicians and journalists have been talking about what to eat and to drink in this country in order to stay alive and not die. What I have to say may sound inappropriate, as the remarks concern me, but it will help to establish the facts. Look at my face. Listen to the way I speak. This is a small fraction of what I have suffered. […] What happened to me was not caused by food or by my diet but by the political regime in this country. Friends, we are not talking today about food literally but about the Ukrainian political kitchen where murder is on the menu. Speaking about murder I would love to name the assassin. […] Don't forget this lesson because you could be next" (Volodarsky, 2009).

Meanwhile, a communication campaign led by professionals and sponsored by Yushchenko's opponents was organized to rule out the possibility of an intentional poisoning. Viktor Pinchuk, President Kuchma's son-in-law travelled to Vienna to meet with the Austrian physicians in the Rudolfinerhaus. Pinchuk proposed to Zimpfer that he would finance what the Rudolfinerhaus would need to manage the press relations. Yffic Nouvellon and Ramzi Khiroun from the Paris office of the media consultency Euro-RSCG followed Pinchuk - a regular customer of Euro-RSCG - to Vienna. On 28 September, international news agencies received a press release asserting that Yushchenko had not been poisoned. The *Financial Times* [London] and *La Croix* [Paris] later revealed that the press release was actually written by Nouvellon and Khiroun who had access to the medical records (Chemin, 2010). Zimpfer cutrelations with the French team after he had been informed of Euro-RSCG's connections with Kuchma.

On September 29, an additional press conference was organized by Nouvellon for Wicke, the Rudolfinerhaus Medical Director, who at first denied that Yushchenko had been poisoned. Five days later, however, Wicke had to sign the following statement : "at present we are investigating the possibility of an external cause of poisoning. It is impossible at the moment either to confirm or to deny whether it was intentional or unintentional. The press release of September 28 according to which poisoning could be excluded is wrong and is refuted by this report." On October 8, a second international press conference was held. Wicke repeated that a "medically forged diagnosis" had been diffused by a person not employed in the clinic, referring to Korpan (Volodarsky, 2009). On October 10, Wicke asserted on the Ukrainian TV Channel ICTV, that neither Korpan nor Zimpfer had informed him of a poisoning. He pointed out that there was no evidence to support these claims and that the clinic should not be involved in Ukrainian politics. Following these assertions, Wicke received death threats that prompted police to organize a permanent armed guard.

On October 1, an additional visit to the Rudolfinerhaus was organized. Epidural analgesia was administered, motivated by dorsal pain. A week later, Zimpfer and Korpan requested the assistance of "international organizations" considering the clinical features exhibited by Yushchenko raised the suspicion of the use of substances that usually belong to biological weapons. Chervonenko, Yushchenko's security chief, reported that Zimpfer told him: "I do not know what has happened to the patient. It could be anything including some form of biological weapon" (Bonnet and Stolz, 2004).

In mid-October, samples of blood, hair and nails were sent to Saathoff, the University of Virginia's Critical Incident Analysis Group [CIAG] in Charlottesville (Kessler and Stein, 2005). A team of experts was established, including Holstege, Director of Blue Ridge Poison Centre, who declared that dioxin was "at the top of his list of culprits". On October 22, the Ukrainian Department of Justice asserted that Yushchenko's serious health problems were the consequence of a herpes infection ([Anonymous], 2004b).

The initial vote for presidency was held on October 31, 2004. Yushchenko obtained 39.87% and Yanukovych 39.32%. Due to the fact that none of the candidates had obtained more than 50%,

a second round of voting was organized for November 21. Election results announced Yanukovych 49%, Yushchenko 46%.

In this second round, multiple voting, extra votes for Yanukovych after the polls were closed and the discrepancy between exit polls and the final results prompted Yushchenko and his supporters to refuse to recognize the results and led to the so-called Orange Revolution that took its name from the colour of the campaign material. At 2am on November 22, Orange leaders broadcast an appeal to citizens to gather in the centre of Kiev, at Maidan Nezalezhnosti. By noon about 100,000 Ukrainians had converged in Maidan protesting about election fraud. Organizers blocked important government buildings. After congratulating Yanukovych, the pro-Russian candidate who had announced his victory, Vladimir Putin slightly changed his mind. He waited for the official announcement of the results. Yushchenko's supporters still camped on Krechtchatik, the city's main street, "despite (freeze frost / ice?) and snow to support their disfigured hero" (Dhombres, 2004). After 13 days of massive popular protests that became known as the Orange Revolution, the Supreme Court overturned the election results and ordered a re-vote of the run-off election for December 26 ([Anonymous], 2004g). Some papers considered that Yushchenko used his chloracne as a (stigma / sign?) of his fight against Russian power, increasing his popularity more than he had done with his original appearance. In these circumstances, Tymoshenko feared that Kuchma and his staff would do their best to cancel the presidential election. The US Department of State also declared its concern and that it expected free elections on December 26 that reflected the will of the Ukrainian people. Finally, Yushchenko did win the re-vote on the second round with 52% of the vote (Mas, 2004).

Evidence and denials of intentional dioxin poisoning

On November 17, 2004, at a meeting of the board of directors of the European Academy of Dermatology and Venereology in Florence, Italy, held just before the 13th Congress, Professor J.H. Saurat (at that time president of the EADV) agreed with all the dermatologists participating in the session that the picture seen on that day's television news was most probably chloracne and the poison, dioxin. This was not quoted however in the minutes of the EADV board (JH Saurat personal communication).

On November 23, 2004, John Henry, a toxicologist at St Mary's Hospital, London, suggested the Yushchenko's severely disfigured face could be related to dioxin poisoning. Henry admitted, however, that he had no toxicological evidence to back up his claim. "My diagnosis is from the photo and from the medical report of him being normal two months earlier. […] Very few medical conditions give this type of transformation in such a short time". Henry also argued that it would be possible to produce the effect seen in Yushchenko's face from a single high dose of dioxin hidden in food.

Nick Edwards, Guy's and St Thomas' Hospital in London was sceptical: “chloracne is a side effect of dioxin exposure but I have not heard of dioxins being used as a malicious chemical agent in this way.” Mandy, dermatologist at the University of Miami in the US, suggested the cutaneous lesions might be rosacea that “can explode under heavy stress and this looks like he has a typically fulminant case” ([Anonymous], 2004l). Lotti, University of Padua, Italy, also questioned the validity of Henry's conclusions, arguing the impossibility of making such a diagnosis by looking at a photo. Lotti added that he would be surprised if anyone were to select dioxin as a poison. “Dioxins have only modest toxicity and you would need an extremely high dose to get chloracne. […] Only kilos of contaminated food, administered over several days, would give you chloracne” (Castellani, 2004). These were considered by experts in the dioxin field as “claims from non-cognoscenti, since half a gramme of dioxin powder in a glass of cognac may have done the job, which had been well confirmed later on” (JH Saurat personal communication)

Meanwhile, Abraham Brower [Biodetection Systems, The Netherlands] proposed testing the blood for dioxin-like compounds. On December 7, he obtained blood samples from Yushchenko collected in Vienna. Using the DR-CALUX [Dioxin-Responsive Chemically Activated Luciferase Expression] bioassay, high levels - over 100 parts per billion on a lipid basis - of dioxin-like compounds were found. However, as the technique measured the response from all dioxin-like compounds, the test could not identify which dioxin substitute was present in the blood sample.

At the same time, two other European laboratories applied gas chromatography mass spectrometry to these samples. The technique confirmed the high dioxin level previously found and specified that the result was entirely due to TCDD without background levels of any other dioxin, furans or PCBs. The amount of TCDD measured was 110 parts per billion [ppb] in blood lipid. i.e. more than 5,000 to 50,000 times higher than the amount present in people living in industrialized countries. In fact, the presence of high levels of only TCDD strongly supported the possibility that the poison originated from a laboratory. Whereas the maximum accepted daily dose in humans is 4 pg/kg body weight (b.w.), Yushchenko was administered a single dose of 20 µg/kg b.w., i.e. 5 million-fold more than the accepted daily exposure. About two milligrams of dioxin have been estimated as the body dose at the time of poisoning (Ryan, 2012).

Thereafter, *The New York Times* noted: “new details of Mr. Yushchenko's hospital admissions in Vienna raise disturbing questions: Was the candidate poisoned or infected with some biological agent, and, if so, with what? What is his current state of health, in the middle of a pivotal battle for power?” (Rosenthal, 2004b). A week later *The New York Times* recalled that “in the earlier years of the cold war, the KGB and the Eastern European intelligence services used poison against some political enemies. In a famous case, a Bulgarian dissident, Georgi I. Markov, was killed with poison in 1978 by the Bulgarian secret service, apparently to silence his broadcasts on the British Broadcasting Corporation. At a London bus stop, an agent using a spring-loaded umbrella injected into Mr. Markov's leg a platinum pellet that contained a dose of ricin. He died after three days of intense fever and vomiting” (Rosenthal, 2004a).

In an interview for *The Times* [London] on December 8, Korpan claimed that the illness was a result of a deliberate attempt on the presidential candidate's life: “This is no longer a question for discussion. […] We are now sure that we can confirm which substance caused this illness. He received this substance from other people who had a specific aim.” When asked if the aim had been to kill him, Dr. Korpan replied: “yes, of course.” On December 11, Zimpfer announced on TV that Yushchenko’s poisoning was caused by dioxin, probably administered orally ([Anonymous], 2004m). “His initial severe abdominal pain suggested that he had eaten the poison. We have proved the source of his problem, and we clearly suspect third party involvement” (Rosenthal, 2004c). A senior official in the Yushchenko camp told *The Observer* [on December 11] that the poisoning was “clearly planned by professionals, perhaps former employees of the KGB.” The source added that the poison was called T-2, or “yellow rain” - linked to dioxins and the former Soviet Union's answer to the US's Agent Orange - and that the CIA had been consulted in trying to identify it.

Siegel, an associate professor at New York University's School of Medicine, considered that confirmation of dioxin in Yushchenko's blood left no doubt that he was intentionally poisoned: “a person's response to dioxin is actually somewhat unpredictable. Some people metabolize it faster than others. […] And yet, his personal metabolism was able to get rid of enough of it so that he survived.” Siegel said that Yushchenko's skin disfigurement, stomach illness, and other current health problems are likely to disappear with time and proper treatment. But Siegel added that prolonged exposure to dioxin raises larger concerns about Yushchenko's future health. “What may happen is, unfortunately, there seems to be evidence that prolonged dioxin exposure increases the risk for cancer” (Synovitz, 2004). Irina Gerashchenko, Yushchenko’s spokeswoman declared in a telephone interview that the diagnosis compelled prosecutors to reopen a criminal investigation into his poisoning. Yushchenko was convinced that what happened to him “was an act of political reprisal against a politician in opposition.” He reiterated that he had been the victim of a murder plot. “I believe now more and more that what happened to me was an act of a settling of political scores. […] The aim was to kill me” ([Anonymous], 2004n).

These statements were not sufficient to convince some people who strongly claim to believe that this “fishy” event was actually a “poison plot fraud” (Raimondo, 2004). Spectacular photos of the effects of dioxin on Yushchenko’s face were published in medical papers (Mégarbane, 2010; Sterling and Hanke, 2005). However, Yuri Ostapenko, head of the Toxicology Information Centre of the Russian Health Ministry, told the Moscow radio station *Ekho Moskvy* that “dioxins do not belong to immediate effect poisons: poisoning develops for years and decades, and so it is impossible to get a dose of dioxin today and get poisoning tomorrow” ([Anonymous], 2004j).

Putin also lambasted the accusations that came from western Europe and the US ([Anonymous], 2004d). Yanukovych’s supporters said the illness was probably caused by bad sushi, too much cognac or a severe case of herpes. Viktor Pinchuk, Kuchma’s billionaire son-in-law, said he did not believe that there was evidence that Yushchenko was poisoned. “I believe he is sure it was poisoning. He’s not a liar. But some people from his camp created this provocation

against him, his image, the government and the country. Rumours pretended that the disease was an ordinary food intoxication and the disfigurement actually caused by injections of stem cells for an aesthetic purpose" (Page, 2004). Wicke, who had "resigned" from his position as Medical Director at the Rudolfinerhaus, repeated his disagreement with what he regarded as an unofficial diagnosis of poisoning: "the first two times Yushchenko was examined there was no evidence of poisoning whatsoever. […] I can tell that the Institute of Forensic Medicine in Vienna did not find any traces of poisonous agents in his blood…If there is no poison, there cannot be poisoning. […] I resent the notion of doctors being pressured to change their medical opinion into statements not backed up by medical evidence for political or financial reasons. […] Dr Zimpfer asked me to change my mind in public. […] I refused to change my opinion without any medical evidence." Consequently, Wicke sued the Rudolfinerhaus for damages (Holt, 2005). In response to this claim, experts quickly pointed out that dioxin can be found only if it is specifically looked for, which had not been done at the Institute of Forensic Medicine in Vienna. The Institute had checked, according to accepted guidelines, the most frequent poisons, a list which does not include dioxins.

The political class in Ukraine did not seem particularly moved by the news, which only seemed to confirm what many Ukrainians suspected already: "in a country used to political assassination attempts, the hypothesis of a murder plot, if it is proven, will be just a new addition to an already long list" ([Anonymous], 2004k).

Yushchenko visited the Vienna clinic again on December 10, where he remained until December 13. When returning home, at Kiev airport, he and his wife Kateryna Chumachenko declared they were definitely convinced of the responsibility of the authorities ([Anonymous], 2004a; [Anonymous], 2004j). Yushchenko added: "the regime lives its very last days […] I compare this period with the fall of the Soviet Union or of the Berlin Wall" ([Anonymous], 2004f).

A commission had investigated the Yushchenko case in October and decided that he had suffered from a combination of a viral infection and several other diseases. Prosecutors had closed the investigation before the second round of voting, considering that they could not determine whether he was poisoned. After the results providing evidence of intentional poisoning were known, Yushchenko praised Prosecutor General Piskun for reopening the criminal investigation into his illness. However, he proposed that the investigation be conducted after the additional voting because he didn't want the vote to be influenced "either positively or negatively" by the inquiry.

On December 13, 2004, Ukrainian prosecutors reopened their investigations into allegations Viktor Yushchenko was poisoned (Lisova, 2004). The commission was led by Sivkovych, a lawmaker who had supported Prime Minister Viktor Yanukovych. "The results of the most recent expertise in Vienna are giving us grounds to renew our work," Sivkovych said. "However, we are not convinced that deliberate poisoning can be proved.[…] all those scenarios are more public relations than truth" ([Anonymous], 2004h).

On December 19, 2004, Victor Yushchenko was presented to the Swiss group led by J. H. Saurat [Geneva].

The inauguration of Yushchenko as Ukrainian President took place on January 23, 2005. In September 2006, Ukraine's prosecutor-general Medvedko announced that investigators had determined the time, place, and circumstances in which the poisoning attempt took place. Two years after the event, he confirmed the results obtained by the Western laboratories. The identity of the individual or individuals remained apparently unknown (Kupchinsky, 2006). Interviewed by *Le Monde* on June 6, 2008, Saurat confirmed the dioxin level initially found, "10,000 times higher than the maximum accepted level. […] It was pure dioxin that could be easily found in numerous laboratories but a non-intentional poisoning is excluded" (Châtelot, 2008).

Intentional poisoning was, however, still denied by some. On June 4, 2008, Zhvaniya, [member of *Our Ukraine*] Yushchenko's former Campaign Director, claimed in an interview with the BBC that the so-called poisoning was nothing more than food intoxication, "all biological investigations have been falsified". Zhvaniya stated that Yushchenko's blood samples were secretly taken to the US, where they were enriched with dioxin and later taken to the UK with help from the US special services (Kupchinsky, 2006). In September 2009, Larysa Cherednichenko, previously in charge of investigations into criminal cases in the Ukrainian Prosecutor General's Office, also said that high-ranking officials from the presidential secretariat and family members of Yushchenko falsified evidence in his poisoning case, with dioxin being added to Yushchenko's blood samples. A special commission even concluded that the Yushchenko poisoning was actually falsified to strengthen his position during the 2004 presidential election. The fraud allegations were dismissed by Ukraine's Prosecutor General.

Victor Yuschenko as a medical case.

Treating an extreme phenotype: the five-year short story from Jean-Hilaire Saurat & Olivier Sorg with the permission of the patient is summarised in four headings:

- How and why did Victor Yushchenko go to Geneva?
- Which were the organs affected?
- Which specific treatments were used?
- How was dioxin clearance speeded up?

How and why did Victor Yushchenko go to Geneva?

On December 19, 2004, Professor JH Saurat, chairman of the dermatology department at Geneva University Hospital, was requested by Yushchenko's wife Katarina to visit him in Kiev. He flew there with two collaborators, Dr Luca Borradori, MD, (now Head of the Department of Dermatology of the University Hospital of Bern) and Dr Olivier Sorg, a biochemist (now the leader

of the dermatotoxicology team at the University of Geneva). At that time, Yushchenko was receiving no medical care, and his health status was found to be very poor.

Prof. Saurat invited Yushchenko to come to the Geneva University Hospital as soon as possible, and explained to the family the strategy he would follow to cope with the dioxin disease. The strategy would include immediate and medium/long term action:

- *In the very short term*, it would be necessary to manage the ongoing effects of the "acute phase" of the acute dioxin exposure, a situation previously not reported in the medical literature. When Yushchenko came to Geneva on January 5, 2005, a very poor status with ongoing extremely painful peripheral neuropathy and several life-threatening endocrinological abnormalities were identified and properly controlled (Saurat *et al.*, 2012).
- *In the medium/long term*, the challenges were:
    - to cope with any new organ dysfunction induced by persistent, extremely high, toxic dioxin levels,
    - to explore any method to speed up dioxin clearance, since this poison was expected to stay above toxic levels for up to 10 years.

Such challenges would necessitate the constitution of a dedicated, focused group with the ability to act on both clinical and scientific grounds. In the absence of previous medical experience with such a type of dioxin exposure, it was felt necessary to try to first scientifically understand the clinical situation with all possible tools, and then adapt therapy accordingly.

The patient and his wife understood the challenge well, and for (up to) five years courageously coped with the, sometimes painful, strategy.

On December 26, 2004, Yushchenko won the new second round of the presidential election, and on January 5, 2005, it was the severely ill, elected president of Ukraine who came to Geneva.

From that day and during the following five years, Prof. Saurat entirely supervised the medical follow-up of Yushchenko, with a dedicated team in the Department of Dermatology, with the help of many consultants in the Geneva University Hospital and with contributions, through confidential mail and phone exchanges, from experts in different fields world-wide. Importantly, a medical team was selected to carry out the daily follow-up in Kiev, which included Dr Roman Fedosyuk, Dr Rostislav Valikhnovskyi, and for the cosmetic follow-up, Dr Olga Bogomolets. Olga Bogomoletz, the head of a private dermocosmetic clinic in Kiev, reported in an interview: "I never met Yushchenko before when a colleague asked me to receive a VIP without giving his name. Yushchenko came and asked me to make his skin lesions less visible. A few weeks later he came back and proposed I become his local cosmetician in the team led from Geneva by Prof. Saurat. I had to travel with him and carry out his daily treatment according to a protocol defined by Prof. Saurat. I had to report the results and participate in the discussions with the physicians involved in his case. I did it until October 2005.[…] I performed minor operations on the skin, sometimes two times a day; sometimes he had 10 or 20 wounds covered with gauze. Although he suffered a lot, I

never heard him complain. […] Immediately after the poisoning, the physicians evaluated that he had only 70% chances to survive, a month later only 10% […]. He lost over 10 kg. The pain lasted about six months. Then he recovered and had to become familiar with his new face. He did it on his own, without psychotherapy" (Guillemoles, 2010).

Which were the organs affected?

Part of this was reported in 2012, in a scientific paper published in The Journal of Toxicological Sciences under the title "The Cutaneous Lesions of Dioxin Exposure: Lessons from the Poisoning of Victor Yushchenko" ((Saurat *et al.*, 2012). We reproduce the summary here since it captures the main points.

"*We followed for 5 years a man who had been exposed to the most toxic dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), at a single oral dose of 5 million-fold more than the accepted daily exposure in the general population. We adopted a molecular medicine approach, aimed at identifying appropriate therapy. Skin lesions, which progressively covered up to 40% of the body surface, were found to be hamartomas, which developed parallel to a complete and sustained involution of sebaceous glands, with concurrent transcriptomic alterations pointing to the inhibition of lipid metabolism and the involvement of bone morphogenetic proteins signaling. Hamartomas created a new compartment that concentrated TCDD up to 10-fold compared with serum and strongly expressed the TCDD-metabolizing enzyme cytochrome P450 1A1, thus representing a potentially significant source of enzymatic activity, which may add to the xenobiotic metabolism potential of the classical organs such as the liver. This historical case provides a unique set of data on the human tissue response to dioxin for the identification of new markers of exposure in human populations. The herein discovered adaptive cutaneous response to TCDD also points to the potential role of the skin in the metabolism of food xenobiotics*"

The organs and systems involved, other than the skin, were just cited in this publication : arthritis, neuropathy, pancreatitis, hepatitis, gastrointestinal inflammation, amongst others. It was mentioned that "*each will be fully addressed in future publications when the mechanism has been better analysed by appropriate ongoing data analysis* : such as anaemia, hyperlipidaemia, endocrine disruption.

Anaemia: During the three years following dioxin intoxication, the blood concentration of red blood cells of Yushchenko was always below normal range. This anaemia could be explained by an increase in urinary *hepcidin* observed in Yushchenko (600 ng/mg creatinine, when normal range is 10-200 ng/mg). Hepcidin up-regulation prevents iron absorption in the gut and transport to the blood, causing anaemia (Viatte and Vaulont, 2009).

The potential role of dioxin-like ligands in the regulation of hepcidin was so far not known.

Hyperlipidaemia. During the three years following dioxin intoxication, the blood concentrations of triglycerides, and to a lesser extent, of cholesterol, were above normal range (Figure 15). A positive correlation between dioxin intoxication and hyperlipidaemia has already been observed in a cohort of Czech workers exposed to TCDD during the production of the 2.4.5-T herbicide in a chemical plant (see § 3.1.3.9) (Pelclova *et al.*, 2001)

Endocrine disruption. According to various studies, the complex of dioxin and its receptor AhR may activate oestrogen receptors and thus acts as an endocrine disruptor (Klinge *et al.*, 1999; Ohtake *et al.*, 2003). Various endocrine parameters were studied during the treatument of Yushchenko. During the first year following TCDD poisoning, blood oestradiol and oestrone were elevated, which correlated with increased SHBG, the binding protein for sex hormones. This indicates an imbalance between oestrogens and androgens at the expense of androgens (Table 1). These data indicate a hyper oestrogenic status. On the thirteenth month after TCDD poisoning, it was decided to treat the patient with letrozole, an aromatase inhibitor used in breast cancer therapy, in order to decrease the production of oestrogens which were suspected being involved in the production of the skin lesions. Indeed, the skin content of oestradiol in Yushchenko was higher than that in control males, and even slightly higher than that of females above 40, and the gene encoding the enzyme aromatase, essential in the production of oestradiol, was induced 10-fold in Yushchneko's skin compared to matched controls (Figure 16). As shown in Table 1, letrozole treatment decreased the levels of oestrogens and SHBG, and increased the levels of testosterone, FSH and LH, the latter two being involved in the control of sex hormone production.

Metabolomic analyses of urine samples from Yushchenko allowed the discovery of 24 putative urinary biomarkers of dioxin exposure, among them various steroids and bile acids (Jeanneret *et al.*, 2014; Jeanneret *et al.*, 2016).

To the best of our knowledge, these observations are unique from a scientific point of view. Of note, even after the cessation of letrozole, there was no recurrence of the signs of hyperoestrogenism.

Blood glucose. During the course of his dioxin-induced skin disease, Yushchenko often had a blood glucose reading between 6 and 9 mmol/L (normal range between 4 and 6 mmol/L), a high value for the C-reactive peptide, and sometimes a high concentration of glycated haemoglobin. A high glycaemia with a high haemoglobin glycosylation, along with a sustained inflammation as indicated by the C-reactive peptide, are characteristic of insulin resistance, although a type-2 diabetes was not formally diagnosed.

Transcriptomics. A whole genome gene expression analysis was performed on blood and skin samples and repeated at various times, between February 2005 and December 2007, and compared to the mean of matched controls (Saurat *et al.*, 2012). Many genes were highly induced or

repressed. CYP1A1, a known gene induced by dioxin, was induced up to 175-fold, and a very high induction persisted for three years. On the other hand, most genes encoding enzymes involved in lipid metabolism, in particular sebum production, were highly repressed (Saurat, *et al.*, 2012).

Which specific treatments were used?

In the absence of previous medical experience with such a type of dioxin exposure, there was no established specific treatment protocol for any organ involved, including the skin. Therefore, we analysed each problem with all possible tools, and then adapted therapy accordingly, sometimes with the need for approval from the committee of ethics of our institution.

Whole body surface surgical procedures

We initially observed that any skin incision(al?) resulted in dystrophic healing, which we found to be a dioxin-induced, very fast skin healing response (Barouti et al., 2009). With this important limiting feature to incisional skin intervention, we found that *mechanical dermabrasion* and *multiple micropunch extraction/aspiration techniques* yielded very quick healing (again due to the mechanism cited above) and were cosmetically still satisfactory. These methods allowed both significant pain relief from inflammation and extraction of large amounts of dioxin-rich hamartomatous lesions. A total of 26 procedures were performed on the whole-body skin surface under general anaesthesia, from month 4 to month 46 after poisoning.

Tumor Necrosis Factor alpha (TNF-α) blockade

Compassionate use of tumor necrosis factor α (TNF-α) blockade was considered because non-steroidal anti-inflammatory drugs and systemic steroids were not effective, when severe, chronic and painful inflammation over large areas of the body skin was the major problem. At that time, the experience with anti-TNF in any indication in dermatology was still limited, and the data we had from our repeated transcriptomic data on Yushchenko's skin and blood rather pointed to an IL17-type driven process, but IL17 antagonists were not available.

The patient received three infusions of infliximab (a chimeric anti-TNF-α monoclonal antibody) but because of intolerance this was then switched to adalimumab (a human anti-TNF-α monoclonal antibody), which was given for 18 months, from month 16 to month 34 after poisoning. The period during which adalimumab blood concentration was maintained at around 10 µg/ml (i.e., 80mg every other week, which is a high dose) corresponded to a progressive but very significant response on the inflammatory component. Generation of new hamartomatous lesions abruptly declined from month 28, but the extent to which this improvement was driven by TNF-α blockade versus the repeated whole body surface surgical procedures is unclear. Adalimumab had to be stopped when a

psoriasiform eruption with patchy inflammatory alopecia occurred, with biological signs of IL17/22 activation in skin and blood. Since that episode, inflammatory hamartomatous skin lesions never recurred.

How was dioxin clearance speeded up?

We had to explore any method to speed up dioxin clearance, since this poison was expected to stay above toxic levels for up to ten years.

The analysis of the decay curve of TCDD in various body compartments led to the confirmation that TCDD is in equibrium between blood lipids and subcutaneous fat. This allows the determination of the TCDD body burden from blood analysis. The comparison of our TCDD decay curve for Yushchenko with a model of the decay curve for individuals not exposed to TCDD shows that in the case of severe intoxication by TCDD, the rate of TCDD elimination from the body is significantly increased (Figure 14).

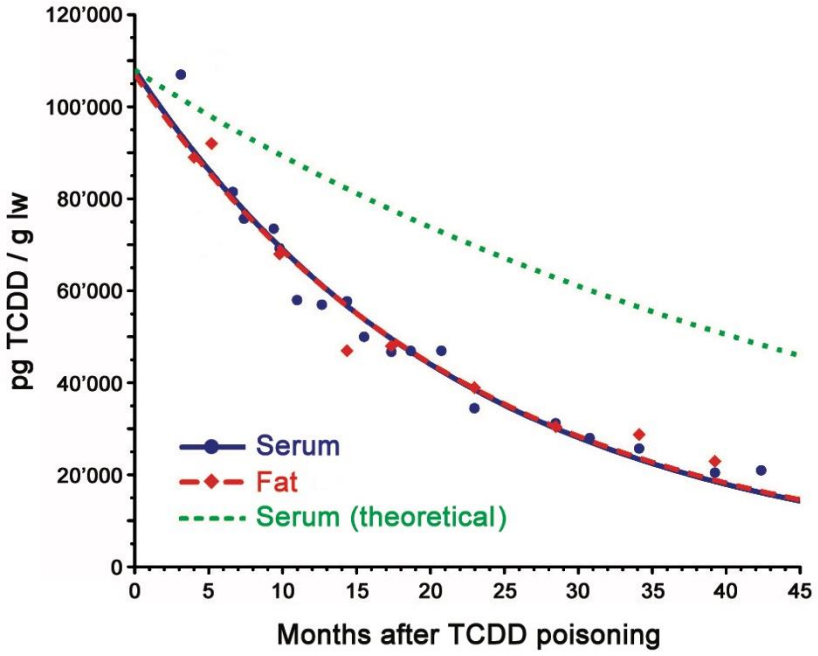


Figure 14. TCDD decay curves in serum lipids and subcutaneous fat for Yushchenko. The green dotted line represents the expected decay curve in serum for individuals not exposed to TCDD (Sorg *et al.*, 2009).

The analyses of many biological samples taken from Yushchenko allowed us to discover the first known TCDD metabolites, 2,3,7-trichloro-8-hydroxydibenzo-*p*-dioxin and 1,3,7,8-tetrachloro-2-hydroxydibenzo-*p*-dioxin (Sorg *et al.*, 2009).

Liposuction

Due to the distribution of dioxin in the adipose tissue (Sorg et al, 2009), we performed liposuction of subcutaneous abdominal adipose tissue in order to increase dioxin clearance. The procedure was

not well tolerated by the patient, with residual pain for three weeks but no constitution of panniculitis. Although dioxin concentrates in adipose tissue, it does notexert any biological effects there due to a lack of active cytokine secretion and AhR signalling pathway.

Orlistat is a gastric and pancreatic lipase inhibitor that limits absorption of dietary fat and therefore increases fat in faeces. We thought that by increasing the elimination of fat in faeces, we would also increase excretion of dioxin bound to lipids in faeces. The patient was given Orlistat from month 11 to month 48 after poisoning, 240 mg per day (with periods with lower dosage due to interference with social and professionnal life). Monitoring of dioxin in faeces showed that most of the dioxin is eliminated from the body by this route (Sorg *et al.*, 2009).

Epilogue

At the time of writing, September 2017, 13 years after poisonning, Yushchenko has survived, has quit politics, lives with a remaining level of dioxin which is probably the highest in the world, but does not suffer any more health problems than the majority of persons of his age in the Western world.

Chloracne, hazardous wastes and municipal solid waste incinerators

Love Canal

Love Canal has been regarded as one of "the most appalling tragedies in American history" (Beck, 1979). The Canal is named after William T. Love "a 1890s visionary and entrepreneur [who] sought to develop a planned industrial community, Model City, in the area. Waters from the Niagara River were to be routed around the Niagara escarpment [the other famous attraction of the region, Niagara Falls] to produce cheap hydroelectric power. Model City never happened, but work on the canal to transport waters from the Niagara River did".

"In 1942, Hooker Chemicals and Plastics Corporation purchased the site of the Love Canal. Between 1942 and 1953 Hooker Chemicals disposed of about 22,000 tons of mixed chemical waste into the Love Canal. Shortly after Hooker ceased use of the site, the land was sold to the Niagara Falls School Board for a price of $ 1.00. In 1955, the 99th Street Elementary School was constructed on the Love Canal property and opened its doors. Subsequent development of the area would see hundreds of families take up residence in the suburban, blue-collar neighbourhood of the Love Canal. Unusually heavy rain and snowfalls in 1975 and 1976 provided high groundwater levels in the Love Canal area. Portions of the Hooker landfill subsided, 55-gallon drums surfaced, ponds and other surface water areas became contaminated, basements began to ooze an oily residue, and noxious chemical odours permeated the area." Five chemicals monitored were chloroform, trichloroethylene, tetrachloroethylene, chlorobenzene and chlorotoluene ([Anonymous], 1978c).

"In April of 1978, the New York Department of Health Commissioner, Robert Whalen, declared the Love Canal area a threat to human health and ordered the fencing of the area near the actual old landfill site. In August, the Health Commissioner declared a health emergency at the Love Canal, closed the 99th Street School, and recommended temporary evacuation of pregnant women and young children from the first two rings of houses around the site. President Carter simultaneously announced the allocation of federal funds and ordered the Federal Disaster Assistance Agency to assist the City of Niagara Falls to remedy the Love Canal site" ([Anonymous], 1998). Further studies have found that more than 300 chemicals were present in the soil and homes, 10% of them being possibly mutagens, teratogens and carcinogens (Maugh, 1979).

The Times Beach and Missouri episodes

In 1971, about 29 kg of TCDD-contaminated waste from a plant in Missouri was applied to soil for dust control in various sites in the eastern part of the State. The unusual occurrence of animal deaths and reports of family illnesses near a horse-riding arena led the CDC to investigate. TCP and

TCDD were identified as responsible for the deaths of the animals. Autopsies performed on horses showed that the liver was affected in all animals [necrosis of hepatocytes, extensive fibrosis, thrombosis of blood vessels]. Moreover, seven children exposed to the soiled arena had various general symptoms including haemorrhagic cystitis, diarrhoea, epistaxis, headaches and skin lesions (Kimbrough *et al.*, 1977).

Besides this episode, an additional event involving TCDD occurred in Times Beach, a residential area, on the banks of the Meramac river, inhabited by more than 2,000 people. As the unpaved streets of the town had been sprayed with TCDD-contaminated oil, investigations were made on soil samples. TCDD contamination was found reaching a peak of 300 ppb. A flood in the main part of the town led to an almost complete evacuation of the inhabitants. Experiments conducted on guinea pigs and rats with contaminated soils showed pathological alterations, including the liver. The CDC recommended that Times Beach not be inhabited because of the dioxin contamination. On February 1983, the EPA announced that the state of Missouri and the federal government would purchase the properties in Times Beach (Tiernan *et al.*, 1985). The residents abandoned the town and it remains uninhabited.

An investigation by questionnaire was conducted on 68 Missouri inhabitants exposed agriculturally to dioxin and on 36 individuals with little or no history of exposure. Neither cases of chloracne or porphyria cutanea tarda nor increased prevalence of diseases were reported in the exposed group. The conductors of the survey stated that "it is conceivable that uptake of dioxin from contaminated soils was generally less than estimated for this study group or that chronic exposures to environmental TCDD have actually induced little or no adverse health effects as measured in this study" (Beljan *et al.*, 1984).

In the early 1970s, three trucking terminals in St. Louis were sprayed with TCDD-contaminated waste oil to control dust. In December 1983, the investigators were contacted by a former worker who developed porphyria cutanea tarda. The man was also found to have multiple lytic lesions of his proximal right femur and pelvis with involvement of adjacent soft-tissue. Biopsy of the right ilium revealed a sarcoma. The editor of the Morbidity and Mortality Weekly Report pointed out, however, that "although this worker was probably exposed to TCDD through cutaneous absorption of contaminated oil and also by inhalation of aerosolized dust containing TCDD, the possible relationship between this exposure and the development of subsequent disease is far from clear" ([Anonymous], 1984a).

In 1993, McConnell et al. published the case of a worker in Missouri exposed to waste oil contaminated with TCDD. This 59-year-old white male actually drove a truck from 1962 to 1981 within Saint Louis for a truck terminal that was found to be contaminated with TCDD. During this period, the patient worked with? contaminated waste oil for dust control for two to three months each year. In 1981, he experienced cutaneous symptoms diagnosed as porphyria cutanea tarda. From August 1982 to December 1983, the patient developed a skin disease consisting of numerous open comedones and cysts on both malar crescents, periorbital areas and over both sides of the

nose. Open comedones were also noted behind the earlobes. Although the pathological examination revealed the existence of normal sebaceous glands the authors proposed the disease be regarded as a probable chloracne. The patient was one of two patients - out of 328 who participated in a survey of truck terminal workers - having a skin disease suggestive of chloracne. In 1983, an angiosarcoma of the thigh was diagnosed that resulted in the death of the patient in September 1984. Due to the rarity of these three conditions - porphyria cutanea tarda, angiosarcoma and chloracne - the authors rejected the hypothesis that they coincided by chance alone. Although the patient did not remember having chloracne before 1983, his daughters reported that initial lesions had occurred as early as 1972 when their father was most exposed to TCDD. According to McConnell et al., the recurrence of chloracne in 1983 would be the consequence of the mobilisation of TCDD from fat during the tumour-induced weight loss the patient experienced (McConnell *et al.*, 1993).

The Valley of Drums

The so-called Valley of Drums site was an area used for waste disposal and drum recycling from 1967 to 1977, located in a rural area 10 miles south of Louisville, Kentucky. The site owner dug pits on site and emptied the contents of waste drums from Area Paint and Coating Industries into the pits. After the owner was prevented from burying solvents, he used soil from the nearby hillsides to cover the disposal pits and stored thousands of drums on site until 1977. The EPA inspected the site in 1981 and discovered 4,000 deteriorating and leaking drums that were discharging pollutants. In 1983, the EPA listed the site on the National Priority List. Site investigations found contamination with heavy metals, ketones, phthalates and PCBs in ground water, surface water and soil in the area ([Anonymous], 1990b).

Municipal solid waste incinerators. Controversies in France

General situation

The hygienist principles that arose from 19th century microbiologic doctrines led to the management of domestic refuse in a manner more appropriate to these innovative views than the storage or fermentation processes previously used. Municipal solid waste incinerators [MSWIs] that burnt refuse and microbes were first installed in England in the 1870s, in industrial cities such as [Manchester, Birmingham, London and Leeds]. Two decades later, there were almost 550 furnaces ([Anonymous], 1893). In the US, the first incineration plants were installed in the 1880s, whereas in continental Europe the first facility was erected in Hamburg in 1895, following the 1892 cholera epidemic (Frioux, 2009).

In Paris, an experiment to incinerate the refuse produced in two areas [arrondissements] was proposed in 1885 (Rochard, 1893). An additional incineration experiment was tested in 1894.

Although issues of hygiene led to incineration being considered as the best way to destroy the 600,000 tons of refuse annually produced in Paris, it was regarded reluctantly by those who insisted on the complementary needs of cities and rural areas and favoured the transformation of refuse into fertilizers ([Anonymous], 1897).

The first furnaces, regularly used, were installed in a Paris suburban area in 1906. Then, in 1930, the first national action to promote the incineration of domestic refuse in small and middle-sized cities was adopted by the Ministry of Health. During WWII the "Vichy Régime" - and in fact all the countries involved in the conflict - favoured the reutilization of refuse for agricultural purpose. After the war, new incinerations plants were installed in large cities. In 1973, the *Journal Officiel* pointed out how efficient and hygienic incineration of urban refuse was and, provided the plants were well built and properly run, without any negative impact on the neighbourhood ([Anonymous], 1973; Frioux, 2013).

In the late 1990s and early 2000s, several sanitary crises alerted the authorities to the possible rise in cancers among the population living in the vicinity of MSWIs. Incinerators actually yield four end products that may contaminate the environment: slag, quench water used for cooling the slag, fly ash collected in electrostatic precipitators and flue gas (Buser *et al.*, 1978; Olie *et al.*, 1977). PCDD and PCDF can be present in fly ash and flue gas as trace components of refuse, or formed from chlorinated precursors or due to an array of thermal reactions from non-chlorinated precursors or inorganic forms of chlorine (Loustenhouwer *et al.*, 1980).

In 1998, the Ministry of Environment revealed that 15 incinerators emitted more than 10ng international toxic equivalency [I-TEQ]/m^3, including one of these [Besançon, Doubs operating from 1971] that emitted more than 16 ng I-TEQ/m^3. It was also shown that from 1980 to 1995 more than 800 cases of non-Hodgkin lymphoma and 110 cases of STS had been observed in the area around the MSWI. Although Viel et al. stressed the need to confirm the data by further investigations, they considered their results could not be explained only by socio-economic considerations or by the presence of the University Hospital in the vicinity of the patients that facilitated the diagnosis of these diseases. The authors also admitted that exposure to various chemicals such as dust and hydrogen chloride could be responsible for the diseases they observed but finally regarded the consistency of their findings for STS and non-Hodgkin lymphomas as noteworthy (Viel *et al.*, 2000).

The most significant crisis related to MSWIs occurred in Gilly-sur-Isère [close to Albertville, Savoie] where the incineration plant was built in 1968. In 2001, the sanitary authorities were alerted to the unusual number of cancers among people living in Grignon, a village close to the incinerator and among people exposed to the fumes of furnaces. Concern and anxiety spread among the population of the area, all the more as some papers alleged that the elevated occurrence of cancers occurred in a single street of the village. The analysis performed, in August 2001, on fumes from the incinerator and in in oil, milk and vegetables, revealed elevated concentrations of dioxin, 14-fold more than the authorized concentration in fat tissue. Between October 25, 2001 and July 1,

2002, 365 farms, 28 villages, including 45,000 people, were actually involved by the dioxin contamination. More than 7,000 animals [cows, sheep, goats] were slaughtered, 2,200 tons of milk, 30 tons of cheese and 12,000 tons of hay were destroyed. Although fruits and vegetables were not affected by dioxin contamination, producers were dramatically affected financiallly due to the psychological impact on consumers (Caprioli, 2004). It was shown that the MSWI at Gilly-sur-Isère did not adhere to safety regulations and that led to the plant being shut down on October 25, 2001. The event remains the worst environmental and economical catastrophe in the area ([Anonymous], 2010a; Stefanovitc, 2010a; Stefanovitc, 2010b).

As far as human health effects were concerned, for the period 1983 to 1999, the mortality among males due to cancers was found to be significantly higher in the studied population compared to other locations in the district ["département"]. Pulmonary cancers and larynx and bladder cancers were the main causes of the deaths. No excess mortality from non-Hodgkin lymphoma or leukaemia was observed. Between 1994 and 2002, 2,055 cases of cancers were recorded?. However no significant excess was observed either for all cancers or for those usually regarded as related to dioxin exposure: STS, non-Hodgkin lymphoma and acute leukaemia in adults. These results, in the end, did not support the hypothesis of an effect of the incinerator on the incidence of cancers in the studied area (Schmitt, 2009).

In 2002, the "Direction Générale de la Santé" contracted with the "Institut de veille sanitaire" to conduct a program for a better understanding of the health consequences of MSWIs ([Anonymous], 2003). A year later, Floret et al. found that the risk of developing non-Hodgkin lymphomas was 2.3 times higher among individual living in the area with the highest dioxin concentration in the vicinity of an MSWI, than among those people living in the lowest dioxin concentration (Floret *et al.*, 2003). In 2004, the Ministry of Ecology ordered the "Comité de la Prévention et de la Précaution" - Precaution and Prevention Committee - to analyse the existing data on the controversial health effects of dioxins and to propose recommendations ([Anonymous], 2004e). A causal relationship between dioxins emitted by incinerators and non-Hodgkin lymphomas was not confirmed. Although the Committee admitted that no argument supported the absence of such a relationship they insisted on the need for additional studies.

Then, from February to June 2005, a national study on serum dioxin and PCB levels in the population was conducted by the National Institute for Public Health Surveillance [InVS] and the French Food Safety Agency [Afssa]. Eight sites located near MSWIs in different districts ["départements"] were involved. About 130 persons per site were included. All of them had been living in the areas for at least ten years and had not been professionally exposed to dioxin, lead and cadmium. As far as dioxin was concerned, their levels were similar to those of other European countries. The people who exhibited the highest values of dioxins were older [serum dioxin levels actually increases with age], frequently overweight and ate more fish than the average. The investigators pointed out that several factors could influence dioxin and PCB levels, regardless of exposure to MSWIs: smoking habits, fluctuation of weight, the presence of an open fire place or

wooden stove at home, urbanization, consumption of foods produced under the plume of an incinerator. The highest serum dioxin levels were actually observed in the vicinity of Senneville-sur-Fécamp, in both unexposed and exposed areas, probably due to seafood consumption in this seaside location. Finally, serum dioxin levels were not found to be significantly higher among people living in the area of the plume of an MSWI compared to non-exposed populations. The investigators concluded that living in the vicinity of an MSWI has no significant effect on serum dioxin levels except for those people consuming local animal food, including dairy products and eggs, or for those who had been living near old incinerators. The authors actually stressed the influence of personal factors, including the consumption of seafood. They also came to similar conclusions with regard to cadmium urinary levels that were not found to be higher among people living near incinerators. Concerning blood lead levels, personal factors and diet had more influence on serum dioxin levels than factors related to incinerators (Fréry *et al.*, 2009).

The first official rules on dioxin emission from wastes were issued in 2000. On December 4, 2000, a European Directive was issued restricting the emissions of dioxin produced by MSWIs to 0.1 ng I-TEQ /m^3 ([Anonymous], 2000b). From December 28, 2005, the value was applicable to French facilities. Many highly polluting incinerators had therefore to be shut down. Due to these rules, from 1995 to 2006, dioxin emissions from incinerators in France have been dramatically reduced, from 1,090 g to 8.5 g annually, whereas in the same time the quantity of incinerated refuse has risen. Lead and mercury emissions also diminished during the same period ([Anonymous], 2012a).

Although old facilities were shut, the adverse health effects of incinerators still remained a matter of concern. In this respect, the incidence of cancers that occurred among adults living in the vicinity of MSWIs between January 1, 1990 and December 31, 1999 in four areas [namely Isère, Haut-Rhin, Bas-Rhin, Tarn] (France) was analysed (Daniau *et al.*, 2009; Fabre *et al.*, 2008). Sixteen incinerators were running during the period. 135,567 cases of cancers were recorded. Significant associations were found among females to find a relationship between exposure to incinerator fumes and overall cancer risk. Relative risks were also found to be raised for breast cancer and non-Hodgkin lymphoma. Whereas the association with non-Hodgkin lymphoma was found significant in both genders, the association between exposure and multiple myeloma was the only significant one found among males. Almost significant relationships were also found with STS and liver cancers in both genders, whereas no significant association was found with lung cancers, bladder cancer, acute leukaemia and chronic lymphoid leukaemia whatever the gender. The authors underscored the unexplained association they found between cancer and MSWI exposure in females. They finally considered that these findings were not sufficient to assert a definite causal relationship between incinerator exposure and cancer, although the results could add convincing elements that supported the adverse health effects of incinerators.

In 2008, Viel et al. published a study on the relationship between non-Hodgkin lymphomas and dioxin emissions from MSWIs in four French departments covered by a population based cancer

registry. They considered cases of persons aged at least 15 years, diagnosed with non-Hodgkin lymphomas between 1990 and 1999 and living in the exposed areas at the time of the diagnosis. 3,974 non-Hodgkin lymphomas cases [2,147 males and 1,827 females] were observed during the period. A statistically significant relationship could be established between non-Hodgkin lymphomas and dioxin exposure for people living in highly exposed areas compared with those people living in slightly exposed zones. The authors pointed out, however, that their results on MSWI dioxin exposure in the 1990s could not be extrapolated to current incinerators that emitted lower amounts of pollutant and are better controlled (Viel *et al.*, 2008b). In an additional study, Viel et al. examined a possible relationship between dioxin emissions from MSWIs and the risk of invasive breast cancers. After comparing 434 cases of breast cancer diagnosed between 1996 and 2002 and 2,170 controls, they could not find any evidence of an association between dioxin emitted from MSWIs and breast cancer risk among younger women (Viel *et al.*, 2008a).

Since 1975, incineration has remained the first way of destruction of domestic refuse. About 23 million tons of domestic waste were produced in 1997 in France ([Anonymous], 1999). Forty-four per cent of them were destroyed by incineration. Despite the dramatic reduction of MSWIs - from 300 in 1990 to 129 in 2010 - France has still the largest number of MSWIs of the European countries. In 2010, France ranked 7th among European countries for refuse incineration.

To the best of our knowledge, no chloracne cases related to MSWIs have been published in France. However, some mild forms of the disease might have been misdiagnosed [Favre and Racouchot disease, for example, see later]. Therefore, the occurrence of chloracne caused by pollutants emitted by MSWIs in people living in their vicinity or professionally exposed cannot definitely be excluded.

As far as chloracne is concerned, Schecter et al. reported one case in a worker employed in a Japanese municipal incinerator. They actually followed two patients who had been working for eight years in an obsolescent incinerator. One of them had chloracne and a PCDD/PCDF toxic equivalency [TEQ] of 360ppt; the other,who did not exhibit skin disease, had a blood TEQ of 278ppt. PCDF accounted for most of the TEQ. Both levels were significantly more elevated than those observed in the Japanese general population. Moreover, the wife of the chloracne patient also had an elevated TEQ level. The authors hypothesized that the contaminated clothes brought home were at the origin of the wife's contamination (Schecter *et al.*, 1999).

Medical investigations in the population of Maincy

by Jean-Hilaire SAURAT and Olivier SORG

In March 2010, the former Mayor of Maincy, a village in the French region of "Ile-de-France", asked Prof. Saurat to help her association to obtain an official acknowledgement from the French authorities that the population of Maincy suffered significant harm as a consequence of the use of a very polluting waste incinerator that had released high amounts of dioxin over many years. Jean-

Hilaire. Saurat and Olivier Sorg decided to conduct a clinical trial in the population of Maincy, matched to control volunteers from the Geneva area (Switzerland) in order to find biomarkers of dioxin exposure. Owing to the very long biological half-life of TCDD (≈ 8 years), a sustained exposure to small amounts of dioxin leads to a persistence of dioxin in the body and might affect various physiological parameters. Histopathological examinations of 59 skin biopsies from the Maincy cohort revealed a normal skin in only 15% of all cases, a non-specific lymphocyte infiltrate in 32% and a perifolliculitis in 44% of cases. Moreover, skin lesions characteristic of chloracne syndrome (Saurat *et al.*, 2012) were observed in 7% of these biopsies. Metabolomic analyses of urine samples from Yushchenko allowed the discovery of 24 putative urinary biomarkers of dioxin exposure; these biomarkers could also discriminate a group of Czech workers highly exposed to dioxin in the 1960s (see § 3.1.3.9), as well as the Maincy cohort, from matched controls (Jeanneret *et al.*, 2014; Jeanneret *et al.*, 2016). These clinical and biological data tend to demonstrate that sustained exposure to a strong pollution from a waste incinerator may have an impact on the health of the population living in the area. Maincy population expose to dioxin finally got some compensation. (Jolly, 2019)

Concluding remarks

The previous pages illustrate how fascinating the history of chloracne is. Starting in the late 19th century with von Bettman's and Herxheimer's observations of a limited number of patients exhibiting a few comedones and cysts looking like acne vulgaris, chloracne has extended its offshoot far beyond the usual scope of dermatology into various fields, including industrial matters, politics, environmental concerns, criminal circumstances, warfare, food poisoning and daily personal activities. Among these circumstances, the explosion at Seveso and the criminal poisoning of Viktor Yushchenko were the most publicized.

The explosion at Seveso in July 1976, remains the "gold standard" of industrial accidents involving dioxin. The images of Seveso's cloud, published both in the general media and in scientific papers, showing the deleterious environmental consequences and the cutaneous effects (burns and chloracne) on people not occupationally exposed, including children, have contributed to the concerns about dioxins. The Yushchenko criminal poisoning illustrated how disfiguring chloracne can be and the severity of the systemic effects of dioxin. It has also contributed to a better knowledge of the pathology and pathogenesis of chloracne. Chloracne as an elusive adverse effect of Agent Orange among Vietnam veterans and on the Vietnamese population has underlined the political, scientific and social aspects of the disease. Besides these, the Yusho and Yucheng episodes have highlighted the occurrence of the adverse effects of dioxin caused by daily consumption of food from contaminated areas.

Since its early description, various chlorine derivatives have been associated with chloracne: polyhalogenated naphthalenes, polyhalogenated biphenyls, contaminants of polychlorophenol compounds [TCP and 2,4,5-T], polyhalogenated dibenzofurans especially tri-, tetra-, penta- and hexachlorodibenzofurans, PCDD, DCA contaminants [TCAB and TCAOB], DDT, TCB (Crow, 1982; Ju *et al.*, 2009). The accident that occurred in Boehringer in 1956, provided the opportunity of showing the responsibility of TCDD, now usually known as dioxin. Coenraads et al. hypothesized that the acnegenic effects attributed to PCN actually arose from undetected contamination by PCDD, PCDF and PCB (Coenraads *et al.*, 1994). Despite the variety of chlorine derivatives that caused chloracne, no difference in the cutaneous features of the disease has been distinguished.

Chloracne, that has now been recognized as one of the most constant and prominent features of TCDD exposure, may actually include various signs: dermatological, internal [liver damage, elevated serum hepatic enzymes levels, disorders of fat metabolism, disorders of carbohydrate metabolism, cardiovascular disorders, urinary tract disorders, respiratory disorders, pancreatic disorders], neurological [polyneuropathy, weakness of the lower extremities, sensory impairment [sight, hearing, smell, taste], psychiatric problems [neurasthenic or depressive syndromes], eyelid

pathology and general symptoms [headache, fatigue, irritability, insomnia, loss of libido] (Huff *et al.*, 1980). According to Dunagin, 85% to 100% of patients who have any of the more severe effects of dioxin poisoning also have chloracne (Dunagin, 1984).

However, although numerous symptoms have been described following TCDD exposure, most of them are actually inconsistent but chloracne is "always a symptom of systemic poisoning and not just a cutaneous affection" (Crow, 1981). In this respect it has been proposed that if there is no history of chloracne, it is highly unlikely that systemic changes will be due to TCDD (Young *et al.*, 1978). Chloracne is, therefore, regarded as "one of the most sensitive indicators of chronic exposure to halogenated compounds" (Taylor, 1979), "the hallmark of dioxin intoxication" (Suskind, 1985).

Appendices

Appendix I. Chloracne seminal observations
[Transl. G. Tilles]

S. von Bettmann, Heidelberg, 1897

The faces of *two patients* were speckled with a infinite number of thin black points located in the pilosebaceous ostia. There were also large comedones on the forehead, external ears, behind them, intermixed with small nodules and pustules […] Large comedones were also visible on the beard area and the scalp […], on the chest, back, lateral aspects of the neck and on the nape of the neck […] The skin of the face looked dark-grey, rough and dry. […] Sebaceous cysts were also visible on the penis […] The patients, previously strong men complained of unusual tiredness, loss of appetite […] Both patients said that their symptoms occurred since they had been in charge of the cleansing of towers filled with hydrochloric acid.

K. Herxheimer, Frankfurt am Main, 1899

Male patient aged 22, the face, neck, back, chest and proximal parts of the limbs were covered with nodules, tubercles, pustules and with an "infinite number of comedones". Some tubercles and nodules were excoriated or ulcerated. Moreover, wrote Herxheimer, since the beginning of the cutaneous disease "the patient had been coughing and spiting. […] He is very thin and does not sleep anymore. […] Two months after the patient left the factory, new tubercles and abscesses still appeared. The general condition of the patient remained altered".

G. Thibierge, Paris, 1899

On March 11, 1899, *Edouard R.*, aged 42, was hired to work in a factory in charge of the production of chlorine by electrolysis. He had to change the tanks filled with sodium chloride, and was therefore exposed to the "dense and green gas leaving the tanks" he was forced to inhale. He left the factory in June 1899. Three weeks later, *Edouard R.* noticed black dots on his face and trunk. In December 1899, "dark corneous comedones appeared on the whole body, more or less in relief, mimicking in some places the effects of a gunshot at a short distance." *[transl G. Tilles]* On the face almost every follicular ostium was filled with comedones, mainly located "on the wrinkles of forehead where they delineated a marked blackish trail." Comedones of various sizes were also observed on the earlobes, neck, trunk, limbs - except palms and soles - and genitalia where they were larger than elsewhere [3-4mm]. The skin of arms was dry and squamous.

G. Thibierge, Ph. Pagniez, Paris, 1900

Didier D., a male patient, aged 34, employed in the factory from February 1899 till August 1899. Ten days after hiring he was afflicted with oedema of the face and could hardly open his eyelids, to such an extent he had to stop his work for several days. Simultaneously, a great number of comedones occurred on his face, the dorsal aspects of hands, forearms, thighs and legs. Five months after he left the factory, the patient still exhibited numerous comedones mainly on his forehead, delineating a 2 cm width, on both sides of the nose extending to the lower eyelids. Many sebaceous cysts varying in size from a pin-head to a piece of lead shot were visible on the anterior, posterior and lateral aspects of the neck, on the posterior aspect of the earlobes, on the scalp, the chest and back. The largest sebaceous cysts were located on the genitalia.

Louis D., male patient, aged 18, was hired to work in the factory in August 1899, in charge of the electrolysis devices. Four months later, he noticed redness and oedema of the face. Then numerous comedones appeared on the scalp; the face and the earlobes became red and sprinkled with comedones. The nose and chin were relatively spared. There were pustules except on the lower part of the cheeks. Sebaceous cysts were visible on the penis. Other parts of the body were less afflicted although not completely spared.

Oscar D., male patient, aged 28, was employed in the factory from February till December 1899, in charge of the cleansing of electrolysis devices. The disease is composed of comedones intermixed with acne indurata on the face, neck, shoulders and genitalia. In fact, all parts of the body but the hands were afflicted. A great number of comedones were observed on the scalp. The face was red and granite-like; the forehead, the cheeks, the earlobes and the back were covered with numerous comedones. Sebaceous cysts were visible on the penis and scrotum.

L. Rénon, C. L. M. Latron, Paris, 1900

On March 1900, *Louis X. male patient*, aged 25, entered Laënnec Hospital, [Paris]. The patient was gaunt and had a bad cough. The clinical examination revealed several respiratory abnormalities. Numerous Koch bacilli were found in the expectorations. From January 1900, the patient had been employed in a factory in charge of the production of chlorinated lime. Five months after he began this activity, his workmates noticed on his head little pimples that progressively spread. From the 6th month, he became increasingly weak. The eruption was composed of black or brown points, the size of a millet seed, surrounded by a bright area. Unna bacilli were recognized on microscopic examination of the comedones. The comedones are disseminated on the forehead; they are mostly confluent on the cheekbones extending to the eyebrow and cheek. Only a few comedones are visible on the nose and on the nasal fold. Many comedones are visible on earlobes. No comedones are present on the rest of the body.

H. Hallopeau, P. Lemierre, Paris, 1900

Eugène L., male patient aged 43, had been working for a year in a factory producing chlorine. Five months after being hired, the patient realized that his skin had darkened; the dark colour lasted, despite vigorous washings. Moreover, he said, many of his workmates complained of the same phenomenon. The strange appearance of his face, "darkened as though it was covered with black carbon" *[transl. G Tilles]* was actually due to the infinite number of comedones mainly located on the cheeks, the nose and retroauricular areas. The wrinkles were underlined by black trails. Touching the skin of these areas gave the feeling of a rasp. The same colour, although lighter, was observed on various parts of the body, mainly on the thighs, arms and legs. The scalp was squamous and the patient exhibited a diffuse alopecia. Inflammatory lesions, papules and pustules were visible on the cheeks, above the upper lip and on the eyelids and nose. On the genitalia, the aspect was quite different: the scrotum was scattered with many sebaceous cysts, the size of a pinhead or of a grain of millet. Every cyst was centred by a tiny hole which released a greasy, white substance when pressure was applied.

H. Hallopeau, Trastour, Paris, 1900

Jules C., male patient, aged 45, was also employed in the factory that produced chlorine by electrolysis. Eighteen months after he left the factory, he noticed white lesions that subsequently blackened. When admitted to the Hôpital Saint-Louis, his forehead, nasal alars and cheeks were covered with comedones. The earlobes and the retroauricular skin were intensely afflicted with comedones, looking like corneous masses. Pustules were visible on the back. There were many sebaceous cysts, some of them quite large, on the penis and scrotum. Comedones were also numerous on the thighs and legs. Since the beginning of the disease, a diffuse alopecia occurred.

P. Fumouze, Paris, 1901

T., male patient, aged 25, had been working for five months in the electrolysis room. He was in charge of the refilling the containers and cleaning them. The first general symptoms appeared five to six days after he began working in the electrolysis room: drowsiness, weakness. The dermatosis appeared five months later: the face was swollen, similar to an erysipelas. Comedones were visible on the nasal alars, cheeks, chin and neck where the first comedones appeared. Three different types of lesions were observed: black dots encapsulated inside the sebaceous ostium, nodules centred by a comedone and suppurated nodules centred by a white dot. The earlobes were red and swollen. An alopecia was also present. A few nodules were observed on the shoulders, arms and forearms. On the back? were many sebaceous dilated ostia that gave the aspect of a cardboard riddled with pinholes.

P. M.., male patient, aged 19, had been working for a year in the electrolysis room. Two months after he began to work there, his face became swollen and red. The eyes disappeared in the oedema. The redness lasted a fortnight and disappeared suddenly and was succeeded by red nodules. Eight months later, the eruption extended to the trunk and genitalia.

L., male patient, aged 40, had been working for 18 months in the electrolysis factory. The first comedones appeared three months after he began his work on electrolysis. They were not preceded by oedema of the face. He spits and coughs. The patient said: "my work makes me sleepy and lazy." He had no alopecia, his skin was rough, exhibited a great number of comedones mainly on the forehead, neck and shoulders. Fumouze wrote he had never observed a patient with such shoulders: "they looked like white shoulders covered with a black lace whose meshes, quite thin, quite tight would be linked by invisible threads." Large nodules without comedones, the size of a pea, were visible on the back?. A great number of comedones were visible on the arms, thighs and legs. Only a few comedones and small sebaceous cysts were visible on the genitalia.

A.D., male patient, aged 34, started work in the electrolysis workshop on August 4, 1889 and left on February 28, 1901. The dermatosis began with an oedema of the face, six weeks after the beginning of the exposure to chlorine. A few weeks later, the acne extended to the whole body. One year later, he left the electrolysis workshop. A few comedones were visible on the nose.There was no alopecia. Numerous comedones were visible on the earlobes and behind them, some of them the size of a pea. Comedones were also visible on the arms and chest. Only one sebaceous cyst was visible on the scrotum.

F., male patient, aged 30. The first cutaneous symptoms - comedones on the face - appeared seven months after his exposure to chlorine gas . He was weak and could hardly stand when he left the factory. Numerous sebaceous cysts were visible on the penis and earlobes. The limbs were spared.

B., male patient, aged 48, had been working for two years in contact with chlorine gas. The first cutaneous lesions appeared behind the earlobes then on the trunk. No sebaceous cysts occurred on the genitalia. His condition was very bad. He had bronchitis and drowsiness. He was very weak and could hardly walk.

J.C., male patient, aged 45, in charge of electrolysis. Three months after starting to work the first cutaneous lesions appeared: comedones around the eyes, back and limbs. Eight months later, chloracne was generalized. After a year, large sebaceous cysts developed on the scrotum and the penis.

L., male patient, 44, was in charge of electrolysis from September 15, 1899 till April 14, 1900. A typical chloracne was visible on the face. Comedones were also present on the neck, smaller than those seen on the face. A few comedones were also visible on the trunk. Hands and feet were spared. Comedones, xerosis and red papules were present on arms, thighs and legs. Sebaceous cysts the size of a hazelnut were present on the scrotum. The hair on the scalp was sparse. When he was

admitted to the Hôpital Saint-Louis [Hallopeau's department], the patient was very weak and slept day and night. The hair was sparse, the face was blackened as though it was tinted with black carbon; the skin was thick and rough. Nodules centred by comedones were visible on the trunk. Large sebaceous cysts were visible on the scrotum and the penis. The limbs were also afflicted with comedones and nodules. Hands and feet were spared. Tuberculosis was diagnosed. The patient became increasingly weak and finally died on February 27, 1901.

R., male patient aged 43: the first symptoms - drowsiness, shivers - appeared three months after the patient entered the factory where he was in charge of electrolysis. Then comedones appeared on the forehead, nose, malar crescents, earlobes, neck and back. Large sebaceous cysts were visible on the scrotum. Comedones were also visible on arms, forearms and thighs. The general condition was altered, the patient was gaunt. He was afflicted with tuberculosis.

A. Jaquet Basel, 1902

Male patient, aged 30, entered the Rheinefelden factory in January 1901. He was in charge of the filling and cleansing of the electrolysis "cells". The first cutaneous symptoms occurred in June 1901: pruritus of the genitalia and abdomen. In November, the face became red and swollen, extending to the neck, earlobes and the upper part of the chest. The nose and forehead were blackened due an infinite number of comedones. A great number of black points were also visible on the ears, the skin of the retroauricular areas of which was speckled with whitish sebaceous cysts. The skin of the back and shoulders felt like a rasp. All the follicular ostia were filled with a small horny comedone, brownish and slightly prominent. Huge comedones were located on the dorsal aspect of the penis. The scrotum was covered with a great number of sebaceous cysts.

Male patient, aged 28, had been working for 15 months before the first cutaneous lesions. A few pustules appeared on the nape of the neck, preceding the extension of the disease to the whole body after a few days. The face was slightly swollen; the skin of the face was blackish. The forehead and the temples were speckled with little black points filling the pilosebaceous ostia. Some comedones were 1mm in diameter. The whole body was regularly speckled with comedones, which were larger on the penis. Numerous sebaceous cysts were visible on the scrotum.

W. Wechselmann, Berlin, 1903

Male patient, aged 35; the cutaneous lesions were first located on the skin of the head and extended to the chest, back and tip of the nose. These were covered with small nodules, pustules and a great number of black comedones. The patient also complained of conjunctivitis, laryngitis and bronchitis. The patient used a solution of chlorinated lime to clean his hands, blackened by pressing nuts in a factory. The skin lesions vanished in a fortnight, after the removal of the chlorine the patient was exposed to. Commenting, Lesser underlines how rapidly the cutaneous lesions had disappeared compared to the duration observed in the cases previously published.

W. Lehmann, Freiburg, 1905

Male patient working for five years in “Elektron-Rheinfelden” and for one year in charge of the electrolysis process. A few months (after what?), he noticed small comedones on his earlobes and forehead. Although he was no longer in contact with electrolysis, the cutaneous lesions worsened. He complained of tiredness, drowsiness and weight loss. Papules were visible on the trunk and arms, whereas nodules and sebaceous cysts were located on the chest and penis. Interestingly, the patient’s wife and youngest child were also afflicted.

J. Nicolas, M. Pillon, Lyon, 1926

B. A., a male patient, aged 25. The cutaneous lesions occurred two months after he entered a factory where he was in charge of stripping metallic pieces with hydrochloric acid. Comedones were almost the only elements present, notably on the face, except the dorsum of the nose. The earlobes and the retroauricular areas were also afflicted. On the trunk, only the shoulders and the chest exhibited comedones. Thighs, legs and arms were spared. A few lesions were visible on the scrotum.

T. K., male patient, was afflicted with acne, which appeared six months after he bagan work in a workshop producing chlorine by electrolysis. The extension of the lesions to the whole body immediately suggested the diagnosis of chloracne. The eruption was mainly composed of comedones or tiny black points tattooing the follicular ostia or huge comedones the pressure of which provoked the outflow of a whitish sebaceous substance. The lesions were mainly located on the face, where they were confluent, except on the tip and the alars of the nose. Numerous comedones were visible on the trunk, buttocks and penis. The arms and forearms looked tattooed. Legs, scalp and hands were spared.

J. Nicolas, J. Lacassagne, Lyon, 1929

A worker professionally exposed to chlorinated naphthalene for 18 months exhibited intense lesions of chloracne characterized by numerous comedones on areas usually spared by acne vulgaris [earlobes, scalp, neck, arms…]

Appendix II. Chloracne events, Milestones

1774: Chlorine is discovered by Scheele.

1872: Synthesis of octachlorodioxin by Mertz and Weith.

Late 19th century: Electrolysis is used for industrial chlorine production in German plants:

1890, Griesheim

1893, Bitterfeld

1897, Ludwigshafen

1898, Rheinefelden.

1899, Herxheimer, Frankfurt: 4 cases. Production of caustic potash through electrolysis of potassium chloride.

1899, Thibierge, Paris: 1 case. Production of chlorine by electrolysis of sodium chloride.

1900, Thibierge, Pagniez: 3 cases. Production of chlorine by electrolysis of sodium chloride.

1900, Hallopeau, Lemierre, Paris: 1 case. Production of chlorine by electrolysis of sodium chloride.

1900 Hallopeau, Trastour, Paris: 1 case. Production of chlorine by electrolysis of sodium chloride.

1900 Renon, Latron, Paris: 1 case. Production of chlorine by electrolysis of sodium chloride and chlorinated lime.

1900: Start of chloro-alkali production in the US [Heribert Dow, Michigan].

1901, Fumouze, Paris: 15 cases. Production of chlorine by electrolysis of sodium chloride.

1901, Bettmann, Heidelberg: 22 cases. Exposure to hydrochloric acid.

1902, Fraenkel, Halle: 1 case. Production of chlorine by electrolysis of sodium chloride.

1902, Jaquet, Basel: 8 cases [all wives and 5 children also affected]. Production of chlorine by electrolysis of sodium chloride.

1903, Lehmann, Freiburg: 27 cases. Production of chlorine by electrolysis of sodium chloride.

1903, Wechselmann, Berlin: 1 case. Production of chlorine by electrolysis of sodium chloride.

1905, Jacobi, Freiburg: 1 case. Chemical process using *p*-chloronitrobenzene.

1912, USA, [quoted by Taylor, 1974]: First cases of chloracne in the USA.

1914, Wahle, Leipzig, [quoted by Braun, 1955]: 2 cases.

1918, Wauer, Berlin: First report of Perna Krankheit. Exposure to perchloronaphthalene [impregnation of clothes].

1925, Nicolas, Pillon, Lyon: 1 case. Production of chlorine by electrolysis of sodium chloride.

1926, Nicolas, Pillon, Lyon: 1 case. Production of chlorine by electrolysis of sodium chloride.

1929, Nicolas, Lacassagne, Lyon: 1 case. Production of chlorine by electrolysis of sodium chloride.

1927, Teleky, Düsseldorf: 33 cases. Exposure to perchloronaphthalene.

1929 : Start of PCB production.

1934, Sulzberger et al., New York City: 3 cases. Exposure to PCN.

1934, Courtois-Suffit, Paris: 6 cases. Exposure to trichloronaphthalene.

1935, Jones, Alden, Atlanta, USA: 23 cases Exposure to PCB.

1936, Fulton, Matthews, Philadelphia : 101 cases [family members also afflicted], exposure to PCN.

1936, Flinn, Jarvik, Washington DC: First 3 fatal cases [hepatotoxicity]. Exposure to PCN.

1936, Kaimer, York, Pennsylvania, [in Drinker, 1937]: 50-60 cases [one fatal]. Exposure to PCN and PCB.

1936: In France, "acne" caused by trichloronaphthalene was added to the list of occupational diseases for which compensation could be obtained.

1936, Schrader, Germany: 4 cases. Exposure to PCN.

1936, Burger, Kühte, The Netherlands [quoted by Grimmer, 1955] : 76 cases. Exposure to PCN.

1937, Butler, Michigan: 21 cases. Exposure to chlorophenols.

1937, Fuss, Ludwigshafen: 3 cases. Exposure to chlorinated diphenyl oxide.

1937-1938, Great Britain [quoted by Braun, 1955]: Three fatal cases [liver atrophy]. Exposure not mentioned

1938, Mayers, Silverberg: 31 cases. Exposure to tri and tetra chloronaphthalenes.

1939, Greenburg et al., New York City: Three fatal cases. Exposure to PCN [manufacture of electrical condensers].

1941, Thelwell-Jones, Widnes, Lancashire, England : 169 cases. Exposure to PCN.

1941, Jones : 37 cases Exposure to PCN.

1941-1945 : US Military research on 2,4-D and 2,4,5-T as warfare agents.

1942: Initiated biological warfare in US.

1943, Good, Pensky, New York City:

52 cases. Exposure to chloronaphthalenes [Halowax® acne, cable rash]

12 cases [one fatal case, first reported in Scotland]. PCN used to chrome plating. [Deaths from yellow atrophy of liver].

Collier mentioned 2 fatal cases in 1935 and 1938.

Two more cases later and 2 further deaths in November 1940 and January 1941.

1943, Kelley: 55 cases. Exposure to PCN [Halowax®].

1944, Wigley, London: 120 cases [one fatal case]. Exposure to PCN [See-kay wax used in condensers manufacturing].

1944, Cotter, New York: 7 cases [two deaths]. Exposure to pentachlorinated naphthalenes.

1944, Connelly, Marsh, Philadelphia : 200 cases. Exposure to PCN in cable manufacture : "cable rash".

1945, Herzberg; 1947, Teller; Berlin: About 15 cases. Chlorinated paraffin food poisoning.

1947, Dussart, Anvers: 56 cases. Exposure to perchlorinated naphthalene.

1948: First US registration of herbicide 2,4,5-T.

1949, Baader, Nordrhein-Westfalen: 10 cases. Occupational exposure to PCP.

1949-1953, Suskind et al, Nitro, West Virginia: 122 + 12 cases. Overheating leading to explosion. Exposure to TCDD.

1950, Spain: 58 cases. Exposure to electric cables [PCN].

1951-1953: First herbicide military applications [Malayan Emergency].

1953, BASF plant, Ludwigshafen, Germany: 102 cases. Overheating leading to explosion. Exposure to TCDD. Up to 1980, 6 cancer deaths were observed: 3 of stomach cancer, 2 of oat-cell carcinoma of the lung, 1 of colon adenocarcinoma. BASF identified "impurities" in the TCP process that cause liver necrosis in rabbits.

1953, Boehringer: 24 cases. Exposure during manufacturing process or handling of TCP.

1953-1954, Kimmig, Schulz, Boehringer, Hamburg: 24 cases. Exposure during manufacturing process or handling of TCP. 31 cases. Exposure to TCP.

1953-1971, Colomb, Hay [1979], Rhone- Poulenc Grenoble : 97 cases [including 17 affected workers in 1956, 21 in another explosion in 1966]. Exposure to TCP during manufacturing process.

1954, Meigs, Albom, Kartin, New Haven : 7 cases Exposure to chlorinated biphenyl [Aroclor®].

1954, Grimmer, Berlin : 3 cases Exposure to PCN.

1955, Grimmer, Berlin : 60 cases. Exposure to PCN.

1955, Bowen, Houston : 1 case [controversial].

1956, Hay, Hooker chemicals [Niagara Falls] : Staff employees. Occupational exposure to TCP

1957 : Sandermann, Stockmann and Casten : Synthesis of tetrabromodibenzo-*p*-dioxin and TCDD. TCDD is recognized as a contaminant of 2,4,5-T and as the chloracnegen.

1957, Bowen, Houston, Texas : 4 cases. Exposure to DDT.

1958, Hubler, Corpus Christi, Texas : 8 cases. Exposure to PCN [Unichrome wax used in chrome electroplating].

1959, Braun, Heidelberg : 123 cases. Exposure to PCN.

1959, Reggiani, Industrie Chimiche Melegnanesi Saronno/Milan : 5 cases. Occupational exposure to TCP.

1960, Diamond-Shamrock, USA : Occupational exposure to TCP.

1960s and/or 1970s : Chemical plant, Illinois, [quoted by Taylor, 1979] : Exposure to TCAOB.

1960s and/or 1970s : Railroad cars delivering herbicide Southern USA [quoted by Taylor 1979] : Exposure to TCAB.

1961, Bauer, Hamburg : 91 cases; exposure to chlorophenol derivatives.

1961 : November 30, 1961 : JF Kennedy gave the approval for the Operation *Ranch Hand*.

1962 [January 10] : First *Ranch Hand* defoliation mission.

1962, Italy : Explosion. Exposure to TCP.

1963, Philipps-Duphar, The Netherlands [quoted by Zack and Suskind, 1980] : Explosion. 93 exposed, 44 chloracne [8 deaths, 6 from cardiovascular diseases, 1 worker without chloracne died from pancreatic carcinoma] Exposure to 2,4,5- T.

1964, Bleiberg, Diamond Alkali : Cases of porphyria cutanea tarda.

1964, Midland, Michigan : 49 cases of chloracne. Exposure to TCDD.

1964-1965, Khimprom, Ufa, USSR : 5 chloracne cases. Occupational exposure to 2,4,5,-T.

1965, Birmingham : 13 cases of chloracne. Exposure to Aroclor®.

1965-1969, Jirasek, Tchecoslovaquia : 80 cases. [4 patients died during the first 5-year follow-up period : 2 from bronchial carcinoma, 1 from arteriosclerosis, 1 from liver cirrhosis]. Exposure to 2,4,5-T.

1966 : Jensen showed that PCB are accumulated in nature.

1967, Newhouse, London : 1 case. Exposure to PCN [Halowax®].

1968, Bolsover, Derbyshire : 79 cases [90 cases in 1973]. Exposure to TCDD. Up to 1980, one worker was known to have died from coronary thrombosis.

1968 : Yusho [rice oil disease]. PCDD/PCDF and polychlorinated quaterphenyls food poisoning [Japan]. Over 1800 chloracne cases numbered by 1971.

1969 [October 29^{h}] : the White House ordered a curtailment of the use of Agent Orange in Vietnam.

1969, Hara, Japan [quoted by Taylor, 1979] : 20-30% incidence between 1953 and 1963. Exposure to PCB [capacitors plant workers].

1970, Soviet Union [quoted by Hay, 1977] : 128 cases. Manufacture of 2,4,5-T.

1970 Bayer, W Germany [quoted by Hay, 1979, 1982] : 5 cases. Exposure to TCP during manufacturing process.

1970 [April 15th] : termination of all US military herbicide. [April 20th] : suspension of the home uses of 2,4,5-T in US.

1970s, Chemical plant, England [quoted by Taylor 1979] : Exposure to TCAOB.

1971 [October 31st] : last US aerial spraying of Agent Orange in Vietnam.

1972-1973, Chemie, Linz [quoted by Hay 1979, 1982] : 50 cases. Exposure to TCP during manufacturing process.

1971, Poland, Diamond Alkali, Newark : 13 cases. Exposure to 2,4-D and 2,4,5-T.

1972-1973, Chemical plant Ohio [quoted by Taylor 1979] : Exposure to TCAOB.

1972, Kleinfeld, Messite, Svencicki, New York City : 56 cases. Exposure to PCN.

1973, Hasegawa et al., Japan [quoted by Taylor, 1979] : Exposure to PCB [capacitor plant workers].

1973-1974, Michigan : 7 cases ["bromacne"]. Exposure to a mixture of three brominated biphenyls through animal food poisoning. January 1973, Paris Peace Accords : end of the United States' participation in Vietnam.

1974, Deeken, Kansas City : 6 cases. Exposure to 2,6-dichlorobenzonitrile.

1974, Bayer/Uerdingen, West Germany : Occupational exposure to 2,4,5-T.

1974-1977, Chemical plant, Arkansas, [quoted by Taylor, 1979] : Exposure to TCAB.

1975, Oliver, London : 2 cases. Exposure to TCDD.

Before 1976, Thomson, Hayward, USA : Exposure to TCP. Overheating leading to explosion.

1976, Ouw et al., Australia : 1 case of chloracne. Exposure to PCB.

1976 [July 10th], Seveso [Italy] : Nearly 200 cases. Explosion. Exposure to TCDD.

1977, Taylor et al., Cleveland : 41 Exposure to TCAOB.

1978, Monsanto, Newport, South Wales : 20 workers exposed to PCP.

1978 : The "Love Canal tragedy", Alsea contamination, Oregon.

1979, Maroni, Milan : 10 cases Exposure to PCB mixture with 42% chlorine content.

1979 : Yucheng oil disease [Taiwan]. PCDD/PCDF and polychlorinated quarter phenyls food poisoning. Over 2000 chloracne cases numbered in 1985. In February 1979, following Alsea studies, 2,4,5-T was banned in US. Only rangeland and rice fields uses remained approved.

1980 [October 22-24], Rome : First Dioxin conference.

1981, Scarisbrick, Martin, Sheffield : Chloracne cases in two plants producing herbicide Diuron and the precursor DCA.

1982, Rodriguez Pichardo, Seville : Chloracne on family members. Hexachlorobenzene, PCP, PCDD food poisoning

1983, Sehgal, India : One case: inhalation of pentachlorophenate. Evacuation of Times Beach

1984 : Public Law 98-542. the VA is required to determine service connections of some disabilities for the Veterans exposed to dioxin in Vietnam. Compensation is provided only for chloracne and porphyria cutanea tarda that occurred with a year of leaving the military.

1985, Barrière, Nantes, France : 1 case, exposure to TCAOB. All uses of 2,4,5-T and Silvex are banned in US.

Cheng et al., China, 1990 : 44 cases Exposure to trichlorobenzene.

1990, O'Malley, Illinois : 45 cases. Workers assigned to PCP production.

1991 [February 6th] : Congress law 102-4 : established presumptive service for veterans present in Vietnam between 1962 and 1975. Thirteen countries including China, US and India banned all uses of 2,4,5-T.

1993, Mc Donagh, UK,: 17 cases. Occupational exposure to dichloroaniline

Coenraads, China, 1994 : 44 cases Exposure to PCP

Swann Hill, Canada, 1996 : Accident in an hazardous waste incinerator. Exposure to PCB.

1998, Vienna, Geusau : The highest level of TCDD ever measured in humans [144'000 pg/g lw].

1999 : One case : Japanese municipal incinerator worker. Belgian crisis of dioxin.

2001 : Stockholm Convention on reduction of POP

2004 [September 5th] : first symptoms of Yushchenko poisoning; [December 11th] : dioxin poisoning is officially announced; [December 17th] : TCDD is confirmed as the only blood agent. [October 31st] : first round of presidential election in Ukraine; [November 21st] : second round of election. Beginning of the Orange Revolution; [December 26th] : Yushchenko won the presidential election.

2007 : So-called "Mozzarella crisis" [Naples, Italy].

2009, Gawkrodger, UK : 7 cases [chemists], synthesis of triazoloquinoxalines [novel polycyclic halogenated compounds].

2010, Passarini, Bologna : 9 cases [chloracne signs, but with normal dioxin-like concentrations in the blood].

2015, Patterson : one case of chloracne-like comedones on a cigarette smoker.

2015, Eyraud, Bordeaux (France) : MADISH : 2 cases in patients with melanoma treated by BRAF inhibitors.

Appendix III. Summary of findings in occupational, environmental and veterans studies regarding the association between specific health problems and exposure to herbicides ([Anonymous], 2012b)

1994

Sufficient Evidence of an Association. Epidemiologic evidence is sufficient to conclude that there is a positive association. That is, a positive association has been observed between exposure to herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, if several small studies that are free of bias and confounding factors show an association that is consistent in magnitude and direction, there could be sufficient evidence for an association. There is sufficient evidence for an association between exposure to the chemicals of interest and the following health outcomes: STS, non-Hodgkin lymphoma, Hodgkin's disease, chloracne, porphyria cutanea tarda [in genetically susceptible individuals]

Limited/Suggestive Evidence of an Association. Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent. There is limited/suggestive evidence of an association between exposure to herbicides and the following health outcomes: Respiratory cancers [lung, larynx, trachea], prostate cancer, multiple myeloma.

1996

Sufficient Evidence of an Association. STS, non-Hodgkin lymphoma, Hodgkin's disease, chloracne and porphyria cutanea tarda [in genetically susceptible individuals]

Limited/Suggestive Evidence of an Association. Respiratory cancers [lung, larynx, trachea], prostate cancer, multiple myeloma, acute and subacute peripheral neuropathy [new disease category], spina bifida [new disease category] porphyria cutanea tarda [category change in 1996].

1998

Sufficient Evidence of an Association. STS, non-Hodgkin lymphoma, Hodgkin's disease, chloracne

Limited/Suggestive Evidence of an Association. Respiratory cancers [lung, larynx, trachea], prostate cancer, Multiple myeloma, acute and subacute peripheral neuropathy, spina bifida in the children of veterans, porphyria cutanea tarda.

2000

Sufficient Evidence of an Association. STS, non-Hodgkin lymphoma, Hodgkin's disease, chloracne

Limited/Suggestive Evidence of an Association. Respiratory cancers [lung, larynx, trachea], Prostate cancer, Multiple myeloma, Acute and subacute peripheral neuropathy, Spina bifida in the children of veterans, Porphyria cutanea tarda, Type 2 diabetes [category changed from 1998], acute myelogenous leukaemia in the children of veterans [category changed from 1998].

2002

Sufficient Evidence of an Association. Chronic lymphocytic leukaemia**,** STS, non-Hodgkin lymphoma, Hodgkin's disease, chloracne

Limited/Suggestive Evidence of an Association. Respiratory cancers [lung, larynx, trachea], Prostate cancer, Multiple myeloma, Acute and subacute peripheral neuropathy, Spina bifida in the children of veterans, Porphyria cutanea tarda, Type 2 diabetes [category changed from 1998].

"Based on the scientific evidence the committee finds there is inadequate or insufficient evidence to determine if an association exists between exposure to the herbicides used in Vietnam or their contaminants and acute myeloid leukaemia [AML] in the children of Vietnam veterans" ([Anonymous], 2002)

2004

Sufficient Evidence of an Association. Chronic lymphocytic leukaemia**,** STS, non-Hodgkin lymphoma, Hodgkin's disease, chloracne.

Limited/Suggestive Evidence of an Association. Respiratory cancers [lung and bronchus, larynx, and trachea], Prostate cancer, multiple myeloma, Early-onset transient peripheral neuropathy, Porphyria cutanea tarda, Type 2 diabetes [mellitis], Spina bifida in offspring of exposed individuals.

"Because there are no epidemiologic data on the length of time after exposure to TCDD ceases during which an increase in respiratory cancer is associated with that exposure, the committee cannot determine a period beyond which occurrence of respiratory cancer could no longer be presumed to be related to exposure to TCDD [that is no upper limits on the latency or presumptive period could be determined.]" ([Anonymous], 2004i)

2006

Sufficient Evidence of an Association. Chronic lymphocytic leukaemia**,** STS, non-Hodgkin lymphoma, Hodgkin's disease, chloracne.

Limited/Suggestive Evidence of an Association. Laryngeal cancer, cancer of the lung, bronchus, or trachea, prostate cancer, multiple myeloma AL amyloidosis [category change from Update 2004*]*, early-onset transient peripheral neuropathy, porphyria cutanea tarda, hypertension [category change from Update 2004*]* Type 2 diabetes [mellitus], spina bifida in offspring of exposed people.

2008

Sufficient Evidence of an Association. Chronic lymphocytic leukaemia [including hairy cell leukaemia and other chronic B cell leukaemias]**,** STS [including heart], non-Hodgkin lymphoma, Hodgkin's disease, chloracne.

Limited/Suggestive Evidence of an Association. Laryngeal cancer, cancer of the lung, bronchus, or trachea, prostate cancer, multiple myeloma AL amyloidosis [category change from Update 2004*]*, early-onset transient peripheral neuropathy, porphyria cutanea tarda, hypertension [category change from Update 2004*]* Type 2 diabetes [mellitus], spina bifida in offspring of exposed people, Parkinson disease [category change from update 2006], ischemic heart diseases [category change from update 2006].

2010

Sufficient Evidence of an Association Chronic lymphocytic leukaemia [including hairy cell leukaemia and other chronic B cell leukaemias]**,** STS [including heart], non-Hodgkin lymphoma, Hodgkin's disease, chloracne.

Limited/Suggestive Evidence of an Association. Laryngeal cancer, cancer of the lung, bronchus, or trachea, prostate cancer, multiple myeloma, AL amyloidosis [category change from Update 2004], early-onset peripheral neuropathy [category change from update 2008], porphyria cutanea tarda, hypertension, Type 2 diabetes [mellitus], spina bifida in offspring of exposed people, Parkinson disease, ischemic heart diseases.

2012

Sufficient Evidence of an Association. Chronic lymphocytic leukaemia [including hairy cell leukaemia and other chronic B cell leukaemias]**,** STS [including heart], non-Hodgkin lymphoma, Hodgkin's disease, chloracne

Limited or Suggestive Evidence of an Association. Laryngeal cancer, cancer of the lung, bronchus, or trachea, prostate cancer, multiple myeloma, AL amyloidosis, early-onset peripheral neuropathy, Parkinson disease, porphyria cutanea tarda, hypertension, ischemic heart disease, type 2 diabetes [mellitus], spina bifida in offspring of exposed people, stroke [category change from update 2010]

Appendix IV. Dioxins and dioxin-like chemicals

Dioxin is the name given to two classes of organochlorine compounds: PCDD and PCDF. They belong to the so-called “dirty dozen” group also known as POP that include cyclodiene pesticides and analogues such as aldrin [pesticide used on corn and cotton], dieldrin [pesticide used on corn and cotton], endrin [pesticide used to control insects, rodents and birds], chlordane [pesticide used on agricultural crops, lawns and gardens] and heptachlor [pesticide used in household and agriculture], DDT [insecticide and acaricide], hexachlorobenzene [pesticide and fungicide used on seeds], mirex [insecticide and flame retardant], toxaphene [insecticide used on cotton], PCB, PCDD and PCDF ([Anonymous]).

Dioxins have in common a similar chemical structure made of two benzene rings interconnected by two oxygen atoms (Figure 18). They differ only in the nature and position of their substituents : positions 1 through 4 and 6 through 9 can be occupied by hydrogen or halogen atoms. So, *tetrachloro* refers to the four chlorine atoms on the two benzene rings [*dibenzo*], *dioxin* refers to the two oxygen bridges holding the benzene rings, *para* designated by *p* describes the position of the oxygen atoms (Hay, 1982a). The skeleton dibenzofurans is closed to the dibenzo-*p*-dioxin except its central furan nucleus (Huff and Wasson, 1974).

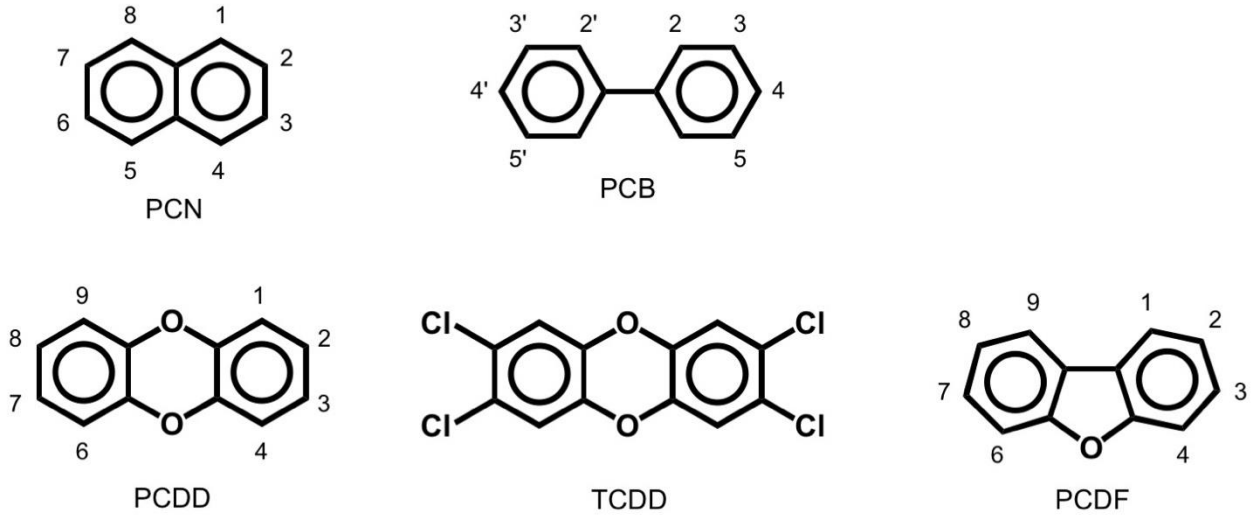


Figure 18. Structures of dioxin-like compounds.

Among more than 400 types of dioxin-related compounds, only 30 of them are considered to have a significant toxicity. It was showed that the toxicity of the various dioxins actually does not depend on the degree of chlorination but on the position of halogen atoms on the outside of the molecule [isomerism]. Of all the isomers, TCDD - sometimes also called “Seveso’s dioxin” – a solid and odourless substance, is the most toxic. It has therefore received the most attention due to its adverse effects on animals, including cancers - with large differences in acute toxicity among

animal species (the guinea pig is 10,000 times more sensitive than the hamster) - that result in its reputation “as a pariah, the Darth Vader of chemicals” the toxicity of which can be compared to that of strychnine (Roberts, 1991a).

Dioxins are not intentionally produced and have no commercial use. They actually are by-products of the alkaline hydrolysis of tetrachlorobenzene with methanolic or ethylene glycolic sodium hydroxide to form TCP that is the industrial precursor of herbicide 2,4,5-T and an intermediate product in the manufacture of the bactericide hexachlorophene (Figure 19). Hexachlorophene was responsible, in 1972 in France, for the death of 36 infants and the intoxication of 200 others, following the use of talcum powder sold under the Morhange trademark. Normally the hexachlorophene concentration in the talc was quite low and had not previously posed any health problem, but during the production of a batch, a worker made a mistake that led to a hexachlorophene concentration of 6%. Since TCDD is a contaminant during the production of hexachlorophene, its concentration was also much higher than usual in this batch of talc, and could have contributed to the overall toxicity of the product.

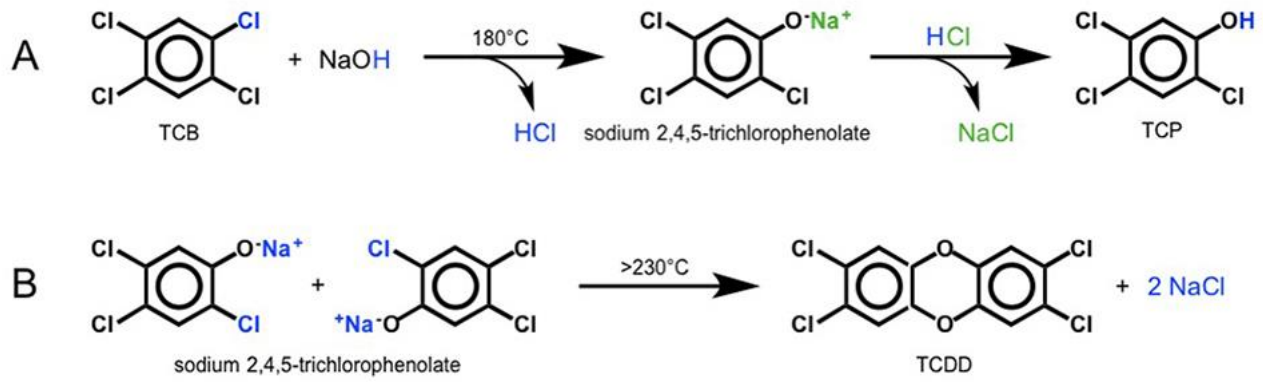


Figure 19. Formation of TCDD during TCP production. A. TCB in ethylene glycol (or methanol) is heated up to 180°C in the presence of caustic soda to form sodium 2,4,5-trichlorophenolate and then TCP following acidification. B. In case the temperature rises above 230°C an exotermic decomposition of the chlorobenzene derivatives occurs, leading to the formation of TCDD.

As seen above, the presence of TCDD as a contaminant was discovered in 1957 when chloracne occurred in workmen involved in TCP manufacture. Production operations were altered to reduce TCDD levels when the industry became aware of the toxicity. Although 2,4-D is chemically related to 2,4,5-T it is generally not contaminated with TCDD.

Prior to industrialization, dioxins existed only in very small amounts due to natural combustion [forest fires] and geological processes [volcanic eruption]. PCDD and PCDF were found in sediments in Siskiwit Lake on Isle Royale, Lake Superior. As there was no anthropogenic input in the basin of the Lake, it was inferred that the sources of these chemicals could only be the atmospheric transport of dioxins and furans (Balzer *et al.*, 2007). Recent works have shown that significant PCDD/PCDF formation had also occurred during the chloro alkali process in the early 20th century. PCDD/PCDF have even been found on the site of a plant where the Leblanc soda

process - employed to produce chlorine and chlorinated chalk - was used from 1840 to 1890 (Weber *et al.*, 2008).

Since the toxic effects of most dioxins and furans are similar, but vary greatly in degree, an internationally accepted method for expressing the toxicity of different dioxins and furans on a common basis has been developed. Toxic Equivalency Factors [TEF] have been assigned to individual PCDD, PCDF and PCB on the basis of how toxic they are in comparison to the toxicity of TCDD that has been assigned a TEF value of 1 (see Table 2 for the TEF values of most PCDD, PCDF and PCB). Once the absolute concentration of all dioxin-like compounds of a sample have been determined, the TEQ value of its dioxin-like content is calculated using the formula :

$$TEQ = \sum_i [PCDD]_i \times TEF_i + \sum_j [PCDF]_j \times TEF_j + \sum_k [PCB]_k \times TEF_k$$

where [X] represents the absolute concentration of a given dioxin-like compound.

Human exposure to all dioxin-like compounds is usually calculated in terms of Toxic Equivalents [TEQ]. The daily intake from all sources of dioxin-like molecules is estimated to be about 0.3-3 pg TEQ/kg (body weight). The maximum accepted dose that can be ingested without health effects is, for some experts, 4 pg/kg daily or 70 pg/kg monthly for others (Webb *et al.*, 1986). As dioxins are highly lipophilic they persist in lipid-rich tissues for a long time and tend to accumulate in the food chain, “the higher an animal is in the food chain, the higher the concentration of dioxins” ([Anonymous], 2016a). Current studies on chloracne point out that the disease may continue to appear even after the exposure to the causal agent has been discontinued; a release of dioxin from fat tissue or hepatic store is hypothesized in such cases.

Dioxins’ half-life in humans has been estimated to be 7 to 11 years with individual variations (Schecter *et al.*, 2006). In fact, the half-life of TCDD ranges from less than five years in people exposed to high doses [more than 10,000 pg/g lipid weight of TCDD in the blood serum] to more than ten years in those people exposed to less than 50 pg/g lipid weight. In Yucheng, PCB and PCDF were shown to be 9 to 46 times higher than those in the general Taiwanese population, 15 years after the food accident. In Seveso, elevated TCDD concentrations persisted in people of the contaminated area 20 years after the event (Baccarelli *et al.*, 2005). In the Yushchenko case, the half-life of TCDD was calculated as 15.4 months the first year following intoxication (Sorg *et al.*, 2009).

The sources of TCDD have been grouped into four categories: incineration sources [municipal waste, hospital waste, hazardous waste, sewage sludge], combustion sources [cement kilns, wood-burning, diesel vehicles, coal-fired utilities, crematoria], industrial sources [pulp and paper mills, chemical manufacturing of herbicides (mainly TCP and pesticides), metal industry] and reservoir sources [biochemical processes, photolytic processes, forest fires, accidental releases]. An additional source of dioxin formation is the closure of the ring system of chlorinated *o*-

phenoxyphenols by a photochemical effect induced by light. These predioxins are quite common in commercial chlorophenols.

Table 2. Code names and TEF values given by the World Health Organisation in 2005 for the most common PCDD, PCDF and PCB.

Family	Compound	Code name	WHO-TEF 2005
PCDD	2,3,7,8-TCDD	D 48	1
	1,2,3,7,8-PeCDD	D 54	1
	1,2,3,4,7,8-HxCDD	D 66	0.1
	1,2,3,6,7,8-HxCDD	D 67	0.1
	1,2,3,7,8,9-HxCDD	D 70	0.1
	1,2,3,4,6,7,8-HpCDD	D 73	0.01
	OCDD	D 75	0.0003
PCDF	2,3,4,7,8-PeCDF	F 114	0.3
	2,3,7,8-TCDF	F 83	0.1
	1,2,3,4,7,8-HxCDF	F 118	0.1
	1,2,3,6,7,8-HxCDF	F 121	0.1
	1,2,3,7,8,9-HxCDF	F 124	0.1
	2,3,4,6,7,8-HxCDF	F 130	0.1
	1,2,3,7,8-PeCDF	F 94	0.03
	1,2,3,4,6,7,8-HpCDF	F 131	0.01
	1,2,3,4,7,8,9-HpCDF	F 134	0.01
	OCDF	F 135	0.0003
Non-ortho PCB	3,3',4,4',5-PeCB	PCB 126	0.1
	3,3',4,4',5,5'-HxCBP	PCB 169	0.03
	3,4,4',5-TCBP	PCB 81	0.0003
	3,3',4,4'-TCBP	PCB 77	0.0001

Dow Chemical Co. – a major manufacturer of 2,4,5-T in the US - suggested that herbicides would actually not be the major origin of dioxin in the environment. Bumb et al. [Dow Chemical's employees] after they had found TCDD in fish from the Tittabawassee River, into which the company poured its effluents, proposed that local and distant sources emitted chlorinated dioxins into the environment. They gathered samples from various sources. As they found chlorinated dioxins in each sample, they concluded that refuse incinerators and fossil-fuelled powerhouses, gasoline and diesel-fuelled automobiles and trucks, fireplaces, charcoal grills and cigarettes are sources of airborne and waterborne particulates that contain chlorinated dioxins (Bumb *et al.*, 1980). As far as cigarette smoke is concerned, Patterson et al. recently published an impressive observation that supports the existence of a relationship with chloracne-like comedones (Patterson *et al.*, 2015). As some high potency polycyclic aromatic hydrocarbons are contained in cigarette smoke, Sorg

considers it reasonable to state that any smokers have a permanent activation of the AhR signalling pathway in their skin that finally leads to MADISH (see above) (Sorg, 2015b).

Dow Chemical Co., therefore, rejected its entire responsibility as a pesticide producer and created the concept of "traces chemistries of fire" according to which the numerous reactions that occur during combustion produce a great number of compounds - including chlorinated aromatic compounds, particularly chlorinated dibenzodioxins, dibenzofurans and polychlorinated bi- and terphenyls - some at very low concentrations emitted in smoke or retained in the ash. Reviewing the various circumstances that could cause the "trace chemistries of fire", Crummett et al. [Dow Chemical] concluded that "it is difficult not to believe that chlorodioxins are entering the environment in trace quantities from very many sources" (Crummett and Townsend, 1984). Finally, concluded Dow, "dioxins have been with us since the advent of fire" (Smith, 1978). As pointed out by Hay, this theory has obviously great advantages for the company as, if true, the finger could no longer be pointed at Dow as one of the major sources of dioxins contaminating the environment (Hay, 1982a).

Most human exposure to low level TCDD actually occurs as a result of eating meat, milk, eggs, fish and related products, as TCDD accumulates in animal fat. In fact 90% of ambient human exposure to dioxin-like compounds occurs through the ingestion of food containing PCB residues (see above). Due to the presence of dioxins in food and the environment, everyone has a certain level of dioxins in the body, leading to the so-called "body burden". Since the mid-1980s, the mean tissue concentration of total TCDD in the general population has decreased by two to threefold. Contamination of human and animal food supplies could also result from improper disposal of waste industrial oils. High levels have also been found in some soils and sediments. Very low levels are found in air, plants and water. Human occupational or accidental exposures have caused tissue concentration of TCDD that are 10 to 100-fold higher than the average background levels in the 1980s. The highest exposures occurred in factories that produced phenoxy herbicides and chlorophenols, while exposure to professional sprayers of these chemicals have been shown to be lower.

Appendix V. Carcinogenicity and adverse developmental effects of dioxins: a controversial matter

As seen above, the first fatal case that affected a worker occupationally exposed to chlorinated naphthalenes was published in the 1930s. Since this (observation???), numerous reports have studied the potential carcinogenicity of PCDD, PCDF and PCB and pointed out how equivocal is the matter.

After Swedish newspapers had reported an alleged increase of lung cancers in railroad workers exposed to herbicides, the controlled study conducted by Axelson and Arundel in 1974 failed to confirm a significant relationship with 2,4-D and 2,4,5-T exposure (Axelson and Sundell, 1974). A few years later, Sterling and Arundel reviewed the epidemiologic studies on TCDD with respect to cancer and pregnancy outcomes. They considered that the conclusions according to which exposure does not cause long-term health effects other than chloracne were not justified. On the contrary, they asserted that "there is an increased risk for cancer." They notably pointed out the increase in the risk of STS, a possible increase in birth defects after paternal exposure and an increase of hydatiform moles after maternal exposure in Vietnam. They admitted that it was unclear which constituents of the phenoxy herbicides were possible carcinogens and suggested that the inconsistencies between the various results might be due to poorly defined exposure data (Sterling and Arundel, 1986). In this respect, Monsanto's reassuring results issued in the late 1970s [see above] were, therefore, all the more put into question since the carcinogenic properties of dioxin had been emphasized by the Swedish authors (Hardell and Sandstrom, 1979). ?

In 1980, in Finland, a group of 30 workers exposed to TCDD-containing herbicides was compared to a match control group: no difference was noted. Another investigation held two years later reported a sevenfold incidence of nasal and nasopharyngeal cancers mainly among wood workers exposed to chlorophenols. In 1984, the AMA overviewed the studies conducted from 1974 to 1981 on railway workers in Sweden and Finland. It suspected an increased risk for malignant lymphoma in workers exposed to phenoxyacetic acid, chlorophenol or organic solvents. Moreover, a proportionate mortality ratio [PMR] analysis of 1,071 deaths in pulp and paper mill workers in New Hampshire during 1975-1985, showed an increase of digestive tract and lymphopoietic tissue cancers. It was hypothesized that the introduction of chlorine during the pulping process might be responsible for the formation of mutagenic or carcinogenic chemicals (Schwartz, 1988).

In 1991, the NIOSH published a major retrospective cohort study of mortality among 5,172 US workers from 12 companies involved in the production of chemicals contaminated with TCDD between 1942 and 1984. Serum levels of TCDD from 253 members working at two factories averaged 233 ng/g lipid compared to 7 ng/g lipid in 79 non-exposed workers. Overall mortality for all causes of death - taken from death certificates - was similar to national rates in the US. Mortality

from STS was non significantly higher than in the reference population. Moreover, a review of tissue specimens from the four workers whose death was attributed to STS revealed that only two of them had true STS. The authors pointed out that the interpretation of the increased mortality from STS was however limited by the small number of cases.

Fingerhut et al. found an unexpected, small but significant increase in mortality from all cancers combined, consistent with a carcinogenic effect of TCDD. Regarding the mortality from non-Hodgkin lymphoma, the authors concluded that their study only suggested a small increase in this risk or no increase at all. They also observed that mortality from other cancers was not significantly higher than expected: liver and stomach cancers, Hodgkin's disease and cancers of the trachea, bronchus and lung. The authors retained two arguments against a carcinogenic effect of TCDD: the absence of significant linear trend of increasing mortality with increasing duration of exposure to TCDD; the study did not assess the effect of TCDD alone due to the fact that the workers were exposed to the chlorophenols and phenoxy herbicides and probably to various others chemicals at the plants. However, the results changed when the cohort was divided into a low-exposure group and a high-exposure group: among the workers with 20 years or more of latency, mortality from respiratory cancers was significantly increased in the high-exposure subcohort; for all cancers combined, mortality, significantly higher than expected in the entire cohort, was more pronounced in the high-exposure subcohort. Fingerhut et al. concluded that the increased mortality especially in the subcohort with one year or more of exposure is consistent with the consideration of TCDD as a carcinogen (Fingerhut *et al.*, 1991). The retrospective study conducted by Manz et al. on employees [1,184 men and 399 women] exposed to TCDD, who worked for at least three months at the Hamburg-Moorfleet plant [see above] also showed an increased cancer risk that, according to the authors, could not be entirely explained by confounding factors and supports the hypothesis that TCDD is a human carcinogen (Manz *et al.*, 1991)

In the late 1990s, an international cohort of 18,390 men and women from 10 countries employed in the production or spraying of phenoxy herbicides and chlorophenols was conducted by the International Agency for Research on Cancer [IARC] and the United States National Institute of Environmental Health Sciences. The mortality from 1955 through 1991 was examined. Among men exposed, mortality from all cancers combined was close to expectation. In the entire cohort, all-cause mortality was lower than expected. The IARC also took into account four studies of herbicide producers [one in the US, one in The Netherlands and two in Germany] and one cohort of residents in the contaminated area in Seveso, Italy. The IARC concluded that there is sufficient evidence in humans for the carcinogenicity of TCDD although, below a certain level of exposure, the cancer risk would be negligible. Indeed, a 35-year follow-up of the Seveso accident did not show an increased incidence of cancer in the population exposed to TCDD in 1976 (Boffetta *et al.*, 2011). Higher relative risks were observed for the groups with the highest measured exposure to TCDD. Concerning lung cancer, it was pointed out, however, that the relative risk of this cancer can result from confounding factors such as smoking. Besides these malignancies, increased risks for other

cancers have been sporadically reported: rectal cancer, breast cancer, bladder cancer, multiple myeloma and myeloid leukaemia. However, the IARC pointed out that the results are not fully consistent. Finally, STS and non-Hodgkin lymphomas are the cancers most convincingly associated with exposure to phenoxy herbicides. There is also increasing evidence that PCBs are human carcinogens. The most consistent pattern of increased risk being for non-Hodgkin lymphomas (Hardell and Eriksson, 2012). TCP is not considered as a human carcinogen.

Besides these cancers, an increased incidence of melanoma in Ranch Hander groups was detected when compared to veterans who served in Southeast Asia without exposure to herbicides. Patterson et al. proposed that patients with cutaneous non-Hodgkin lymphomas, STS including dermatofibrosarcoma protuberans and leiomyosarcomas, should be screened for a history of Vietnam service or industrial exposure to TCDD (Patterson *et al.*, 2016).

In 1982, an interview-administered questionnaire survey was conducted among wives of Dow Chemical's Michigan employees who had been potentially exposed to dioxin, in order to determine whether adverse pregnancy outcomes could be associated with paternal exposure to TCDD. A worker was considered as exposed if he had been assigned to a specific job for at least one month in the chlorophenol process between January 1939 and December 1975. Nine hundred and thirty male employees were identified. An equal number of controls were selected from male employees who had not been exposed to the same chemical process. Among the males, in the exposed group, 586 had wives for interview; 370 of them agreed to participate. Although the investigators admitted that their survey might have ignored differences, they concluded that "under the conditions of this study, there is no biologically meaningful associations between adverse pregnancy outcomes and paternal dioxin exposures" (Townsend *et al.*, 1982).

As far as possible health consequences of maternal TCCD exposure is concerned, Sweeney et al. pointed out that the cumulative evidence does not support effects on infant birth weight, gestational length or increased risk for spontaneous abortion. However, according to the authors, the relationship between both maternal and paternal exposure and risks of congenital abnormalities remains questionable. Concerning a possible relation between TCDD exposure and delayed onset of puberty, the authors encouraged further investigations (Sweeney *et al.*, 2012). According to the Word Health Organization, TCDD does not affect genetic material ([Anonymous], 2010b).

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