Open chemical combustions resulting in a local increased incidence of orofacial clefts

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Abstract

Hypothesis: The open chemical combustions in Zeeburg, Amsterdam, The Netherlands, during the years 1961 up to and including 1969, resulted in a local increased incidence of orofacial clefts during this period.

Study: A retrospective observational epidemiological study was performed, comparing the trend of the incidence of non-syndromal orofacial clefts during the sixties, for the Zeeburg maternity with that of the Wilhelmina Gasthuis. Both clinics were situated in Amsterdam, but varying in distance and compass direction from the incineration works. Thereafter, the addresses of the mothers giving birth to infants with orofacial clefts were plotted on a map of Amsterdam.

Results: Of the 8803 children born in the Zeeburg clinic during this period, 21 had a non-syndromal orofacial cleft, producing an average incidence of 2.4 per 1000 births. For the years 1963 through 1965 the incidence rose dramatically to peak at 7.1 per 1000, before plateauing at an average incidence of 1.68 per 1000 births, still 155% higher than in the Wilhelmina clinic (average incidence of 0.66 per 1000 during the years 1966 through 1969). During the 10 year period the Wilhelmina clinic exhibited no such rise. The incidence of non-syndromal orofacial clefts at the Wilhelmina clinic at no time exceeded 2.3 per 1000 births during the 10 year period. The addresses of the mothers of the Zeeburg clefts were grouped primarily to the northwest (and a smaller group to the west) of the incineration works.

Conclusion: A relation between the open incineration of the chemicals and a local increased incidence of orofacial clefts seems very likely. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

While researching an article on epilepsy and congenital defects in 1973, Koppe and her colleagues serendipitously discovered what seemed to be a surprisingly high incidence of orofacial clefts during the 1960s, in the Zeeburg area of Amsterdam, The Netherlands. This high incidence was not indicative of the incidence at a maternity clinic (the Wilhelmina Gasthuis) elsewhere in the same city (Koppe et al., 1973). Much later it was discovered that chemicals had been incinerated in the open air in the vicinity of the Zeeburg maternity clinic, at the Diemerzeedijk, during the 1960s. A coincidence?

From literature sources and our ongoing studies on possible effects of dioxin exposure on the growth and development of children, we have become aware of the (possible) teratogenic and/or carcinogenic effects of these environmental pollutants. We therefore hypothesised that the local increased incidence of orofacial clefts was a direct result of the open incinerations of the chemicals at the Diemerzeedijk incinerator.

1.1. The diemerzeedijk waste site

The company responsible for the incinerations, which took place from 1961 to 1973, was allocated the “Diemerzeedijk” terrain in 1961. Commissioning commenced...
shortly thereafter. It was soon apparent that a tremendous demand existed for such an incinerator, and major multinational companies, many of whom were later to deny the fact, exploited the opportunity in order to dispose of chemical wastes. The incinerations must have proved lucrative, for the quantities of incinerated chemicals increased phenomenally. The incineration company promptly began importing waste chemicals for combustion from all over Europe, from countries such as Germany and Cechoslovakia, and even from as far as Finland. A scanty registration of the quantities combusted was kept (Table 1). (However, these figures have been shown to be up to 70% understated)!

While the rapidly increasing activities were probably favourable to the incineration company, this was not so for many residents of the surrounding urban areas. Innumerable complaints regarding the extreme smells and air pollution were made. Whilst the incinerations (one to three thousand tons per time) took place merely once every one to three months, it was noted that on the days that they took place, sedimentation powders fell over the surrounding areas. This more than likely was also a consequence of the manner of incineration: the 100 l drums of chemicals were lined up, to at times more than a hundred metres long, tens of metres wide and eight to ten barrels high. A number of the drums were then pierced, allowing the contents to flow out and this was then ignited. According to the official report of the City of Amsterdam (DOW GRM, 1987) this was quite an impressive scene to witness, with drums flying high into the sky as the chemicals and drums exploded! The thick pitchblack smoke columns, more than 100 m high, were visible from tens of kilometres away. The fire department was notified before the chemicals were ignited.

The incineration company was found to be in violation of environmental legislation during the years of operation. This eventually led to the City of Amsterdam taking over the responsibility and drastically reducing the incinerations, and finally decommissioning the waste site in 1973.

Since then, the site has been found to contain numerous toxic chemicals and in toxic concentrations. Anno 1998, a quarter of a century after its closure, the Diemerzeedijk complex remains a prohibited terrain – this as a result of the toxicity. Anglers are prohibited from fishing in the vicinity of the Diemerzeedijk, for fear of their possible ingestion of the contaminated aquatica.

2. Method

Analysing possible environmental influences on the health and well-being of individuals has, in the past proven a difficult challenge. With the advent of modern technological advances, many occupational health hazards have been plotted. For the “uncontained, unisolated” environment this has been more problematic, and animal studies, while indicative, are not perfect, because of well documented interspecies variations (Bracken, 1997). It was therefore decided to test the clinical observation by way of a retrospective observational epidemiological study. The trend of the incidence of orofacial clefts at the Zeeburg maternity clinic, for the period 1960 up to and including 1969, was compared with the quantities of combusted chemicals during this same period. Thereafter the trends of the incidence of orofacial clefts were compared at two maternity clinics in Amsterdam, The Netherlands, over the ten year period from 1960 up to and including 1969. Finally the addresses of the mothers who gave birth to children with orofacial clefts were plotted on a map of Amsterdam.

Table 1

The quantities of chemicals incinerated at the Diemerzeedijk incinerator, 1960–1973

<table>
<thead>
<tr>
<th>Year</th>
<th>Quantities of incinerated chemicals</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>1961</td>
<td>Unknown</td>
<td>Terrain allocated to the incineration company</td>
</tr>
<tr>
<td>1962</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>1963</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>1964</td>
<td>Unknown</td>
<td>Complaints of extreme smells and air pollution</td>
</tr>
<tr>
<td>1965</td>
<td>4235 tons</td>
<td>Incinerations only permitted by south westerly winds</td>
</tr>
<tr>
<td>1966</td>
<td>8574 tons</td>
<td></td>
</tr>
<tr>
<td>1967</td>
<td>9061 tons</td>
<td></td>
</tr>
<tr>
<td>1968</td>
<td>11,789 tons</td>
<td></td>
</tr>
<tr>
<td>1969</td>
<td>Unknown</td>
<td>Under management of the city of Amsterdam</td>
</tr>
<tr>
<td>1970</td>
<td>2500 tons</td>
<td>Under management of the city of Amsterdam</td>
</tr>
<tr>
<td>1971</td>
<td>2500 tons</td>
<td></td>
</tr>
<tr>
<td>1972</td>
<td>2500 tons</td>
<td></td>
</tr>
<tr>
<td>1973</td>
<td>Cessation</td>
<td>Cessation of incineration activities</td>
</tr>
</tbody>
</table>

*a The quantities up to 1968 have been shown to be up to 70% understated (see text) (DOW GRM, 1985).
All the pregnancies at a maternity clinic in Zeeburg, Amsterdam, The Netherlands, situated nearby the waste incinerator mentioned above were reviewed from the medical log books. Each pregnancy was sufficiently documented. The number of orofacial clefts was noted. In order to exclude syndromal clefts, other abnormalities were also noted, as were specifications such as gender. These data were then related to the total number of births, live and stillborn.

The same procedure was performed for another maternity clinic, Wilhelmina Gasthuis, also situated in Amsterdam, The Netherlands, yet in the west of the city, about 12 km away from the waste incinerator (the wind in The Netherlands is mostly from the south-west).

It is important to note that births in the Zeeburg clinic were on social indications only, for example, mothers who had no appropriate room at home for the delivery. Any pathologic pregnancies were sent to the Wilhelmina clinic, where specialized centers for mother and child were available. The Wilhelmina clinic births were thus both on social and on pathological indication.

3. Results

From a total of 8803 births in Zeeburg, in the period 1 January 1960 up to and including 31 December 1969, 22 babies had a non-syndromal orofacial cleft (Table 2). Thus an average incidence of 2.5 per 1000 births. In 1963, 973 infants were born in Zeeburg, of which 5 with an orofacial cleft, producing an incidence of 5.1 per 1000 births. In Zeeburg in 1964, 990 infants were born, of which no less than 7 with an orofacial cleft – an incidence of 7.1 per 1000 births. In the years 1963 and 1964, 3 and 2, respectively, of the cases of orofacial clefts were of cleft palatum molle (soft palate). The incidence of orofacial clefts for the years 1963 and 1964 were statistically significantly higher for the Zeeburg clinic than for the Wilhelmina clinic.

In the maternity clinic Wilhelmina Gasthuis a total of 21078 infants were born from 1 January 1960 up to and including 31 December 1969, including 25 with a non-syndromal orofacial cleft (Table 3). Therefore the average incidence of orofacial clefts over the ten year period was 1.2 per 1000 births. In 1963 the incidence was 1.0, with 2 of 2100 babies born with a non-syndromal orofacial cleft. In 1964, 2187 infants were born, of which 5 had an orofacial cleft, producing an incidence of 2.3. At no time during the ten years from 1960 up to and including 1969 did the incidence of infants born with an orofacial cleft rise beyond 3.0 per 1000 births (Fig. 1).

All the addresses of the mothers who gave birth to children with an orofacial cleft were uncovered with the exception of one of the Zeeburg population and ten of the Wilhelmina population. When the addresses of the children born with an orofacial cleft in the Zeeburg clinic were plotted, there was a remarkable dispersion. No less than 14 of the 24 children were born to mothers living to the northwest of the Diemerzeedijk. There was also a smaller grouping to the west of the incinerator. When the addresses of the children born with an orofacial cleft in the Wilhelmina clinic were plotted, they were far more spread out across the city of Amsterdam, as would be expected.

4. Discussion

4.1. Confounders

While it is no longer possible to reliably control for further confounders, it is arguable that this is not needed. While smoking in the 1960s was not widespread amongst women in The Netherlands, the Zeeburg clinic population

### Table 2

The incidence of orofacial clefts at the Zeeburg maternity clinic for the years 1960 up to and including 1969

<table>
<thead>
<tr>
<th>Year</th>
<th>Total no. of births</th>
<th>CLP</th>
<th>CPS</th>
<th>Syndromal cleft</th>
<th>Total no. of clefts</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>894</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>Sister also had an orofacial cleft</td>
</tr>
<tr>
<td>1961</td>
<td>996</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>Sister also had an orofacial cleft</td>
</tr>
<tr>
<td>1962</td>
<td>1119</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1963</td>
<td>973</td>
<td>2</td>
<td>3</td>
<td>–</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1964</td>
<td>990</td>
<td>5</td>
<td>2</td>
<td>–</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>1965</td>
<td>860</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1966</td>
<td>758</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1967</td>
<td>929</td>
<td>–</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>1968</td>
<td>711</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1969</td>
<td>573</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>8803</td>
<td>14</td>
<td>8</td>
<td>2</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

*CLP = cleft lip with or without cleft palate, CPS = cleft palatum molle (soft palate).
would certainly not have had a greater number of smoking mothers than the Wilhelmina clinic. The socio-economic statuses of the two populations was similar. Both populations were generally from lower socio-economic groups. This also formed the basis for their social indications for giving birth in a clinic, and not at home – there was no suitable room at home for this purpose and/or the parent(s) had insufficient funds for the more expensive hospitals or for home delivery. The selection between delivery in the Zeeburg clinic and the Wilhelmina clinic (apart from pathology and suspected pathology) was based on the residential address of the mother, and on the availability of rooms in both clinics.

This reasoning can also be applied to possible genetic confounders. Neither population was an enclave, and therefore the gene-pools would not have been restricted. While the genetic backgrounds (especially for TGFα) would not be expected to be different for the two populations, any known genetic risk factors would have been indications for delivery in the Wilhelmina clinic.

Furthermore, the use of anti-epileptica could be offered as a possible confounder. A pregnant woman with epilepsy was a pathological condition. Such women would have given birth at the Wilhelmina clinic, and once again, certainly not the Zeeburg clinic. This was also a major reason why Koppe et al. (1973) selected the

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Table 3
The incidence of orofacial clefts at the Wilhelmina Gasthuis maternity clinic for the years 1960 up to and including 1969a

<table>
<thead>
<tr>
<th>Year</th>
<th>Total no. of births</th>
<th>CLP</th>
<th>CPS</th>
<th>Syndromal cleft</th>
<th>Total no. of clefts</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>2364</td>
<td>3</td>
<td>–</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1961</td>
<td>2353</td>
<td>4</td>
<td>–</td>
<td>3</td>
<td>7</td>
<td>1 CLP is sibling of an epilepsy patient</td>
</tr>
<tr>
<td>1962</td>
<td>2381</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1963</td>
<td>2100</td>
<td>2</td>
<td>–</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>1964</td>
<td>2187</td>
<td>4</td>
<td>1</td>
<td>–</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>1965</td>
<td>2129</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1966</td>
<td>2095</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1967</td>
<td>1947</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1968</td>
<td>1804</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1969</td>
<td>1718</td>
<td>1</td>
<td>–</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21078</td>
<td>21</td>
<td>4</td>
<td>10</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

a CLP = cleft lip with or without cleft palate, CPS = cleft palatum molle (soft palate).

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Fig. 1. The trend of the incidence of non-syndromal orofacial clefts for the Zeeburg and Wilhelmina clinics, for the years 1960 up to and including 1969.

- per 1000 births (live + stillborn)
- year

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*This is an example of a citation from the text.*
Zeeburg population as a control group, and the Wilhelmina population as the exposed group in their study on epilepsy and congenital abnormalities.

A difference in alcohol consumption between the Zeeburg and Wilhelmina populations would, for the same reasons as smoking (vide supra), be unlikely. In addition, it was not usual for women to drink alcohol during the 1960s, and this was certainly so for women in the lower socio-economic classes (both Zeeburg and Wilhelmina populations) who would have found it difficult to afford the price of regular alcohol consumption.

Finally, we must consider vitamin deficiencies. There was a shortage of food in the Amsterdam region, during and after World War II. Calorie-wise this was rapidly corrected after the war but a shortage of folic acid might have lasted longer. Yet, a vitamin deficiency would have meant that the pre-war high incidence of anencephaly would have remained high. To the contrary, the incidence dropped dramatically before and during the sixties, and the socio-economic circumstances improved greatly (Romijn and Treffers, 1983; Romijn et al., 1982). Thus vitamin deficiencies could not reasonably be offered as an explanation for the extraordinary results.

An increased concentration of other chemicals, such as PAH’s, and of heavy metals have also been found in the vicinity of the incineration complex (DOW GRM, 1987). We have not considered them in the current study because we could not find evidence in a medical literature search for a link between such substances and orofacial clefts. Other (possible) health effects of these substances are beyond the scope of this article.

4.2. Comparison

As Fig. 1 graphically illustrates, the incidence of orofacial clefts in the Zeeburg maternity clinic showed a relatively gigantic surge in 1963–64. The very atypical trend of incidence over the ten year period, with the peaking in 1963–64 was clearly not indicative of the incidence elsewhere in the same city. This can also be seen in Fig. 1. The Wilhelmina Gasthuis trend displays an incidence of between 1 and 3 cases per 1000 births. The Zeeburg maternity population was a group selected on optimality regarding favourable, healthy pregnancies, with little chance of pathology. This in contrast to the Wilhelmina clinic where approximately half the population group was selected on possible or probable pathology. It is therefore to be expected, contrary to what was found, that there would then be a higher incidence of orofacial clefts in the Wilhelmina clinic than in the Zeeburg clinic. This can be seen in the fact that the average incidence of orofacial clefts in the Wilhelmina clinic (1.66 per 1000 births) is higher than the 1.47 per 1000 births reported for The Netherlands (Derijcke et al., 1996).

4.3. Airborne pollution

Research has pointed out that the incineration processes at the Diemerzeedijk produced large amounts of sedimentation powders, many of which were carried by the wind. Many of the chemicals combusted by the company are known to produce dioxin and dioxin-like sedimentation powders, easily carried by the wind. Eyewitness reports have verified that indeed powdery sedimentations were often seen in the vicinity of the Diemerzeedijk during incinerations (DOW GRM, 1987).

Table 1 shows the registered incinerated chemical quantities from the waste incinerator for the same time period, 1960–1973. Incineration activities were only permitted when the wind was blowing from the south west (DOW GRM, 1987). The reasoning being that any residues would be blown over the IJssel Lake, as opposed to over the urban areas to the south and west of the terrain.

The collected eels and rabbits from the vicinity of the combustion terrain were shown to have toxic concentrations of dioxins in their bodies (DOW GRM, 1987). Additionally, the Dutch Ministry of Water Affairs, in a separate report concluded that there was an increase in the concentration of PCB’s in the bordering IJssel Lake (DOW GRM, 1987), and this while bearing in mind that PCB’s, due to their hydrophobic nature, are poorly transported by water. Was this increase a result of airborne PCB pollution or due to leakage?

The wind in The Netherlands is normally from the southwest, but often comes from the southeast and east. Assuming that the company only combusted the chemicals while a south-westerly wind was blowing. Residues and sedimentation powders would then be blown east and north-east, over a lake, the IJssel Lake. What if the wind changed direction during the day, or if the company, in violation of the stipulations, decided to combust while the wind was blowing from the south-east or east? These same residues would then be blown north-west and west over urban areas of Amsterdam. It is then very interesting to find the atypical groupings of orofa-
Orofacial cleft anomalies are relatively common with an incidence of 1–2 per 1000 births, with a higher prevalence amongst males than females (Derijcke et al., 1996).

Animal studies with mice elicited cleft palate and hydronephrosis in TCDD, a dioxin, exposed embryos. It was postulated that exposure to a teratogenic dose of TCDD led to disturbed proliferation and differentiation of palatal cells. TCDD is known to bind with the Ah receptor (AhR) and thereby alter transcription of specific genes. AhR is found in palatal epithelial and mesenchymal cells, and has its highest expression in epithelium thereof. Furthermore, AhR mRNA and protein were found to be downregulated in mice palates exposed to TCDD (Abbott, 1995). These studies add credence to the proposed relationship between the open chemical incinerations at the Diemerzeedijk and the alarming increase in the incidence of orofacial clefts in Zeeburg during the 1960s.

Couture et al. (1990) examined human palatal shelves exposed to TCDD and concluded that exposure to high levels of TCDD would need to occur in order to alter palatal development. Abbott and colleagues recently stated that they have found evidence for a regulatory system by which human palates could be less sensitive to TCDD than mice palates (Abbott et al., 1998). It must, however, be remembered that these studies were performed with in vitro palatal tissue, and this may be different from the in vivo situation. Furthermore, these studies do not necessarily negate our findings and our hypothesis. While overt signs of dioxin toxicity, such as chloracne, were not evident, chronic high doses of dioxins and at crucial moments during embryogenesis may still very well have caused palatodysgenesis in a number of infants in the Zeeburg area.

4.6. Other midline defects

While researching the incidence of orofacial clefts we noted that a large number of babies born in the Zeeburg clinic had midline defects. This we found surprising, baring in mind that the Zeeburg population was selected on optimal, healthy pregnancies, and that any indications of pathology were reason for the birth to take place in the Wilhelmina clinic. The incidence of central nervous system (CNS) defects (the majority being spina bifida in the Zeeburg group) and of genital defects (the majority being hypospadias in the Zeeburg group) are displayed in Table 4. As can be seen, the incidences fall within the normal incidence range (approximately 3 CNS defects per 1000 births and approximately 1 genital defect per 300 births).

However, in view of the population selection, are these incidences possibly too high? Interestingly, when we plotted the residential addresses of the children born with CNS and genital defects, the vast majority lay to
1. There were numerous complaints of sedimentation powders as a result of the incineration works.
2. Many of the chemicals combusted are known to produce dioxin- and dioxin-like sedimentation powders when combusted, as well as other chemical compounds.
3. There was an increased PCB concentration found in the vicinity of the Dimerzeedijk have toxic concentrations of dioxins in their bodies.
4. Dioxins readily pass the placental barrier, collecting in adipose tissues. 2,3,7,8-tetrachlorodibenzo-p-dioxin: recent advances to-wards understanding the mechanism. Teratology 42, 619–627.
5. Chemical agents can be causative of orofacial clefts, for example a higher incidence of orofacial clefts was found amongst smoking mothers, amongst mothers exposed to glycol ethers, and amongst the offspring of Vietnam-war veterans (American and Vietnamese) exposed to the dioxin-based defoliant, Agent Orange (Sterling and Arundel, 1986).
6. The Zeeburg population was a population selected on optimality regarding health and pregnancy yet demonstrated a very atypical trend and incidence of orofacial clefts for the years 1960 up to and including 1969.
7. Vitamin deficiencies, smoking mothers, genetic enclaves and anti-epilectica could not reasonably be offered as confounders or explanation for the abnormal trend and distribution of the orofacial clefts.

Let us now summarise what we have found and some of the findings found in a literature search:
1. There were numerous complaints of sedimentation powders as a result of the incineration works.
2. Many of the chemicals combusted are known to produce dioxin- and dioxin-like sedimentation powders when combusted, as well as other chemical compounds.
3. There was an increased PCB concentration found in the IJssel Lake, and eels and rabbits collected from the vicinity of the Dimerzeedijk have toxic concentrations of dioxins in their bodies.
4. Dioxins readily pass the placental barrier, collecting in adipose tissues. 2,3,7,8-tetrachlorodibenzo-p-dioxin, or TCDD, a dioxin, is known to produce hydnonephrosis and orofacial clefts in mice. TCDD is known to bind to the aryl hydrocarbon receptor, a receptor seen in high concentrations in epithelial tissues (which also make up the human palate and lip).
5. Chemical agents can be causative of orofacial clefts, for example a higher incidence of orofacial clefts was found amongst smoking mothers, amongst mothers exposed to glycol ethers, and amongst the offspring of Vietnam-war veterans (American and Vietnamese) exposed to the dioxin-based defoliant, Agent Orange (Sterling and Arundel, 1986).
6. The Zeeburg population was a population selected on optimality regarding health and pregnancy yet demonstrated a very atypical trend and incidence of orofacial clefts for the years 1960 up to and including 1969.

### References