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# Iron Project



## Submission to the Department of Health and Children



North Western Health Board
In association with
Sligo Institute of Technology
Trinity College Dublin
NUI Galway

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# 1 EXECUTIVE SUMMARY

Routine sampling over the last ten years in the North Western Health Board region has shown areas with extremely high levels of Iron and Manganese in the drinking water. Of the population of the region, over 160,000 people are served by public water supplies and the remaining 50,000 by private wells and group water schemes. These sources regularly exceed the Maximum Allowable Concentrations (MAC's) of both elements often to a very large extent. This problem is not confined to the North West and other counties exceeding MAC values include Meath, Cavan, Roscommon, Monaghan, Mayo, Kerry and Offaly.

- At present there are no international guidelines relating to the maximum levels of these substances above which health may be affected.
- It is not clear whether a sustained high iron intake from drinking water may affect the health status of the general population and particularly those with hereditary hemochromatosis.
- Hereditary hemochromatosis is a very common condition of abnormal metabolism of iron. The double recessive gene is carried by approximately 1:200 of the Celtic population and approximately 1:8 are carriers. Both of these groups will absorb more iron than the general population.
- It is possible to identify asymptomatic persons by genetic testing and begin treatment before iron overload occurs. Early diagnosis and treatment restores normal life expectancy. From reviewing the literature it has not been possible to identify population studies on areas with high levels of iron in drinking water.
- This study aims to detect areas of high, intermediate and low levels of iron in the drinking water and to compare the populations in terms of iron status. The prevalence of genetic and acquired iron overload will be mapped in relation to the areas where high iron levels have been identified in relation to drinking water.
- At present there is insufficient evidence to determine if high iron levels in drinking water have detrimental effects on population health and this study will provide information to inform and advise the relevant government departments on

the consequences of sustained high iron levels in water used for human consumption.

# 2. BACKGROUND

## 2.1 Iron excess in water supplies in the north west

The European Community Drinking Water Directive 80/778/E.E.C., sets maximum admissible concentrations (MAC values) for over fifty parameters in drinking water aimed primarily at protecting public health. The E.U. when deciding upon MAC levels for parameters takes into account the Guidelines for Drinking Water Quality (World Health Organisation) and the views of the E.U. Expert Committee on Toxicology and Eco-toxicology. The functions of the Environmental Protection Agency of Ireland (E.P.A.) in the field of drinking water quality relate to the assessment and statutory reporting of the activities of the Local Authorities (water providers) in the implementation of the 1988 Drinking Water Regulations. This function is fulfilled primarily in the compilation and publication of an annual report entitled "Drinking Water Quality in Ireland".

Where a public water provider i.e. Local Authority is unable to maintain standards within the MAC values the Minister may, upon application, grant a "departure". This can be given where it can be demonstrated that there is no threat to human health and where the higher concentration of a particular parameter exists naturally in water due to climatological or geological factors which make the standards difficult to attain. The function of granting derogations or "departures" from the standards laid down for parameters that are without health significance to the consumer rests with the Minister for the Environment and Local Government.

In 1998 the Minister granted Sligo Corporation a "departure" for iron and manganese in respect of the town water supply "Kinsellagh" which serves in the region of 10,000 people.

## 2.2 Water sampling

Of the population in the region (210,872 in the 1996 census) over 160,000 people are served by a public water supply (ref. EPA). The remaining 50,000 have access to drinking water through group schemes or private wells. Public water supplies are chemically sampled once per month by the North Western Health Board on behalf of Leitrim County Council, Sligo County Council, Donegal County Council and Sligo Corporation. Group Water Schemes are not routinely monitored for microbiological and chemical analysis although in recent years most would have been sampled annually. The identity of all group water schemes is not fully known. Private wells are sampled on demand and more so in recent years so that owners may avail of national grant assistance. The results of private water sampling are not usually included in the E.P.A. Annual Report and as such would not be within the public domain.

## 2.3 The chemical quality of drinking water in the North West

Iron, manganese and colour excesses feature prominently in data for the North West. Occurrence and fluctuations in levels are naturally influenced and vary greatly. These regularly exceed MAC levels, often to a very large extent. (c.f. Map in Appendix 2)

The MACs for iron and manganese are 200 μg/litre and 50 μg/litre, respectively. These concentrations are based on aesthetic considerations and not health concerns as iron and manganese are not considered to be toxic at these levels. In fact there are no guidelines relating to maximum levels above which health may be affected. In private water supplies (well water) the highest levels have been recorded. The results for private water supplies in the region are shown in Appendix 4 .

The iron and manganese levels are extremely high in parts of the North West reaching values of 50,490μg/l for iron and 8,500μg/l for manganese. The greatest levels are found in private water supplies estimated to serve in the region of 20,000 – 25,000 people. The W.H.O. have not produced a health based guideline value for iron nor does it propose so to do. The type of iron found in a particular environment is primarily dependent upon the geology of the area and a discussion of environmental considerations is included in Appendix 3.

## 2.4 Iron (Fe) in Drinking Water

The EPA Report of 1998, 'The Quality of Drinking Water in Ireland' shows that 8% of all samples of drinking water from public supplies, which were analysed across the country, did not conform to the permitted Maximum Admissible Concentration in respect of iron. The Report showed that 28% of sample results for public water supplies in Counties Sligo and Leitrim and 17% of sample results in Donegal did not conform to the MAC. Other public supplies across the country, which exceeded the MAC values, included Monaghan, Galway, Meath, Bray and Dundalk.

Results of drinking water sampled throughout Ireland for 1998 showed that 13% of group water schemes and 33% of private wells were in excess of the MAC value in respect of iron (EPA Report, 1998). By comparison, results from group scheme water sampling for Donegal for the same period showed that 21% of them exceeded the MAC value. Sample results from group schemes for 1998 in respect of Leitrim were not available to the EPA, but results of sampling by Board staff showed a comparatively high percentage of samples in excess of the MAC. Sample results for private well water in Donegal over the 1998 period showed a greater failure rate than the national average of 33%.

Other group schemes and private well water supplies across the country exceeding the MAC values include Meath, Cavan, Roscommon, Monaghan, Mayo, Kerry and Offaly.

**In general, the degree to which levels of iron exceed the MAC values in public water supplies is not significantly high. However, untreated supplies (which include many group water schemes) and private wells have been shown to be greatly in excess of the Maximum Admissible Concentration levels.**

## 2.5 Manganese (Mn) in Drinking Water

The EPA 1998 Report indicates that of all drinking water supplies analysed for which results were notified, 8% exceeded the MAC in respect of Manganese. Both Sligo Corporation and Co. Donegal public supplies recorded excesses above the national average - 17% and 15% respectively. Nationally, other public supplies such as Cavan, Wicklow and Monaghan have failure rates higher than those recorded in the Northwest.

The Report showed that of all the drinking water samples analysed for Manganese from group schemes and private wells for which results were notified, 13% and 45% respectively were above the MAC. Results for group water schemes in Co. Sligo showed that 19% had levels above the national average. Although the EPA did not have comprehensive results for Leitrim and Donegal, tests on group schemes carried out by the Board over the corresponding period showed a high percentage of results in excess of the MAC. Private well water sampled by the Board showed high failure rates overall, with levels well in excess of those recorded in public water supplies.

## 2.6 Health Implications of Exposure to Iron and Manganese

Iron is a trace element found in meat products (liver and red meat) and plants (dark green leafy vegetables, peas and beans). Between 10mgs-15 mgs of iron are required in the daily diet. Once absorbed, the only way iron is lost by the body is through blood loss.

It is known that toxicity can occur as a result of Hereditary Hemochromatosis, a common genetic disease of abnormal metabolism of iron which appears to be greatly underdiagnosed in this country. Acquired hemochromatosis can develop from multiple blood transfusions, iron-loading diseases and possibly from excess ingested iron. Toxicity can occur, very rarely, from excessive dietary intake. The evidence suggests that, for most people, there is little or no risk of developing iron overload by iron absorption from the diet, even when the diet is fortified with iron. There is, however, some debate about this point in the literature.

There is little or no evidence of the toxic effects of ingested manganese in humans. Most of the evidence on manganese toxicity refers to the inhaled route and occupational exposure.

The WHO Guidelines for Drinking Water Quality advise that levels of iron in water of approximately 2000 µg/l 'do not present a hazard to health'. The WHO concludes that drinking water with values above 2000 µg/l will not usually be drunk due to its taste and appearance. Accordingly, it has not given a health related guideline value for iron, nor does it propose to do so. Neither is it clear from the research data available whether the consumption of water with iron in excess of 2000 µg/l is harmful to health.

# 3. HEREDITARY HEMOCHROMATOSIS (HH)

Hemochromatosis is a condition of abnormal metabolism of iron and is characterised by excess absorption of iron from the diet. It is the most common genetic disease known to science. The double recessive gene to develop the condition is carried by approximately 1:200 of the population and therefore it is not rare. Approximately 1:8 people have the single gene and are carriers of HH. Those with the double gene absorb too much iron and those with the single gene absorb more than a normal person. Studies of normal populations show that the prevalence of iron overload is about 0.5%: a figure that reflects the prevalence of HH. It is not known what proportion of those with the double gene go on to develop symptomatic hemochromatosis.

Once absorbed, iron is not lost from the body unless there is bleeding. It is not known how much storage iron is necessary to cause disease. HH causes iron overload even with a normal diet. Hemochromatosis is rare before middle age. It is important to note that many iron-overloaded patients have no symptoms at least until they are in the advanced stages.

Iron overload affects the entire body with:

- Slate/bronze coloured skin
- Neurological problems (memory loss, vertigo, Alzheimer's disease, Parkinson's disease and tardive dyskinesias)
- Pituitary failure and endocrine problems (hypothyroidism and diabetes)
- Cardiomyopathy, cardiovascular disease, arrhythmias and conduction disturbances
- Cirrhosis
- Hepatoma occurs in about 30% of patients with cirrhosis
- Pancreatic cancer
- Impotence
- Arthritis and chondrocalcinosis

## 3.1 Diagnosis

The most useful laboratory measures for determining whether an individual is abnormally accumulating iron are serum ferritin concentration and transferrin saturation, preferably in combination. Individuals found to have elevated iron levels using these laboratory screening tests are candidates for the hemochromatosis DNA test.

## 3.2 Treatment

Hemochromatosis is treated by a phlebotomy regimen to remove excess iron. This method is highly effective and safe. If phlebotomy treatments are initiated prior to tissue damage, serious complications can be prevented and life span may be normal.

DNA testing has proved invaluable in population studies of the incidence of hemochromatosis. Furthermore, it has been proposed that all newborn children should be routinely tested for this very common, easily detected inherited disease which is highly amenable to effective treatment.

## 3.3 Hemochromatosis DNA Test for Gene Mutations

DNA testing for HH, using the polymerase chain reaction (PCR) ensures fast, effective, definitive, early diagnosis of the condition and ensures the prevention of symptoms through treatment by phlebotomy.

Hereditary hemochromatosis is associated with two disease-causing mutations in the HFE gene (chromosomal locus 6p21).

## 3.4 C282Y

The major mutation, Cys2B2Tyr (commonly known as C282Y), is present in the homozygous state (two copies of the mutation - C282Y/C282Y) in 93% of Caucasians with clinically diagnosed hemochromatosis. The frequency varies in other ethnic groups.

The C282Y/C282Y genotype is highly penetrant, most individuals will develop clinical iron overload if they live long enough. The severity of symptoms resulting from iron overload is also high in this group. Phenotypic expression, as expected, is lower among women than men as a result of menstrual blood loss and childbirth.

Heterozygotes are individuals who carry only one copy of the C282Y mutation (C282Y/normal). They tend to have elevated concentrations of serum iron and ferritin and transferrin-saturation values that exceed normal. It has been suggested that they are at a slightly increased risk of developing iron overload and HH. Some conditions are known to predispose these heterozygous individuals to hemochromatosis. These include haemolytic anaemia, excessive alcohol intake, viral hepatitis, and porphyria cutanea tarda. It is possible that heterozygotes exposed to high levels of iron in their food and water supply may develop the symptoms of hemochromatosis. It is proposed that this possibility will be investigated as part of this present study.

## 3.5 H63D

A second mutation in the HFE gene, His63Asp (commonly known as H63D), somewhat increases the risk of iron overload when it is present together with the C282Y mutation. Of these compound heterozygous (individuals with one copy of each mutation C282y/H63D), 0.5-2.0% will go on to develop clinical evidence of iron overload. Homozygotes for the H63D mutation (H63D/H63D) have a lower risk of developing HH.

It is possible that exposure to elevated levels of iron in the drinking water may increase the risk of developing the clinical symptoms of HH.
The investigation of the effects of high levels of iron in drinking water on the causation of disease in these homozygotes is particularly important. This is because the H63D mutation is very common in the general population. It has been suggested that the frequency of heterozygotes may be as high as 1 in 5.

In summary, is not known what the health implications of high iron concentrations in the drinking water might be on homozygotes (C282Y/C282Y or H63D/H63D) or on the different categories of heterozygotes (C282Y/normal, C282Y/H63D,

H63D/normal). More importantly, it is not known whether disease incidence can be lowered, by reducing the iron level in the water supply or whether it would be more effective to carry out a DNA screen in these areas and manage the disease by treatment.

# 4 AIMS AND OBJECTIVES

## 4.1 Aim

To measure and compare the iron status in populations in the North Western Health Board area exposed to differing levels of iron in drinking water and to measure specified health effects.

## 4.2 Objectives

- To identify areas with high, intermediate and low levels of iron in the water.
- To measure the prevalence of both genetic and acquired iron overload in these areas.
- To assess the impact of high dietary iron, including water, intake on serological indices.
- To investigate the clinical penetrance of hemochromatosis.
- To advise the relevant government departments of the public health consequences of high iron levels in water used for human consumption.

# 5 METHODOLOGY

## 5.1 Summary of Methodology

- Literature review (c.f. Appendix 5)
- Consultation with physicians, environmental health officers, statistician, geneticist, geologist and the Department of Health and Children.
- Set up a project management team (c.f. Appendix 1)
- Define parameters and devise questionnaire
- Submit protocol for ethical approval
- Public information
- Sample selection
- Blood sampling and administration of the questionnaire
- Inputting and analysis of data
- Publication of the results
- Implementation of the recommendations

## 5.2 Literature review (c.f. Appendix 5)

**5.3** Consultation with physicians, environmental health officers, statistician, geneticist, geologist and the Department of Health and Children.

**5.4** Set up project management team which is outlined in Appendix 1.

**5.5** Define parameters and devise a questionnaire. Several relevant areas outlined below need to be addressed in an administered questionnaire.

i. Food history
Iron intake in terms of supplements and diet
Alcohol/ coffee/ tea intake
Vitamin C intake

ii. Drug history-antacids/other

iii. History of blood donation/transfusion

iv. Gynaecological history

Parity

Menstrual history

Contraceptive use

v. Status of water supplies /public supply/private/group scheme

vi. Duration of residence in current location

**5.6** Ethical approval will be sought for this proposed research from the ethical committees of Letterkenny and Sligo hospitals.

**5.7** A public information campaign will seek to advise GP's and the public of the aims and objectives of the project.

**5.8** Sample selection

A map has been drawn up showing areas of high (>2000 μg/l), intermediate and low (<2000 μg/l) iron levels as detected on routine sampling by the environmental health service (c.f. Appendix 2) The sampling unit is a household, given anticipated shared home exposure to iron. A water sample will be taken under appropriate conditions from each household for testing.

In sampling individuals there are several options available. These include sampling one, two or all members of a household. Sampling two members allows for a reasonably powerful statistical analysis and reduces the logistical and cost implications. The samples should represent all adults over the age of 18yrs and both sexes.

In view of the differing sources of water supply (mains, wells and rural water schemes) stratified sampling will be required.

Stratification will be based on an urban versus rural divide and will include low urban iron exposure, low rural exposure and high rural exposure. This is assuming there is no high iron urban exposure.
Taking 1 per 200 as a probable level of genetic exposure then the required number of persons to be sampled would exceed 5000. If two persons per household are acceptable then 2,500 households would be sampled with a distribution divided equally between the three strata.

It is assumed that homozygotic individuals are uniformly geographically distributed in the region. For logistical reasons a form of cluster sampling would be desirable. Because this is a population screening study individual patients will not be identified or followed up and recommendations will be made on the basis of analysis of population figures.

**5.9** Blood sampling and administration of the questionnaire will be performed by trained staff recruited for the project.

<u>Proposed blood testing strategy for this study</u>

a) Serology:

Functional compartment:

Iron

% transferrin saturation and/or TIBC

Serum transferrin receptors[1]

Full Blood Count (FBC)

Transport compartment:

FBC

Storage compartment:

Ferritin

Other tests to be included:

C-reactive protein (CRP)[2]

Alanine aminotransferase (ALT)[3] and/or aspartate aminotransferase (AST)[3]

1. The primary function of the cellular transferrin receptor is to bind to diferric transferrin and to internalise it by receptor mediated endocytosis.
2. Serum Ferritin is an acute-phase reactant. The CRP level will be estimated to establish whether elevated serum ferritin levels are due to inflammation.
3. ALT and/or AST serum levels are often, but not always, abnormal in patients with hemochromatosis. However, abnormal results suggest the presence of fibrosis, cirrhosis, or other complicating factors in combination

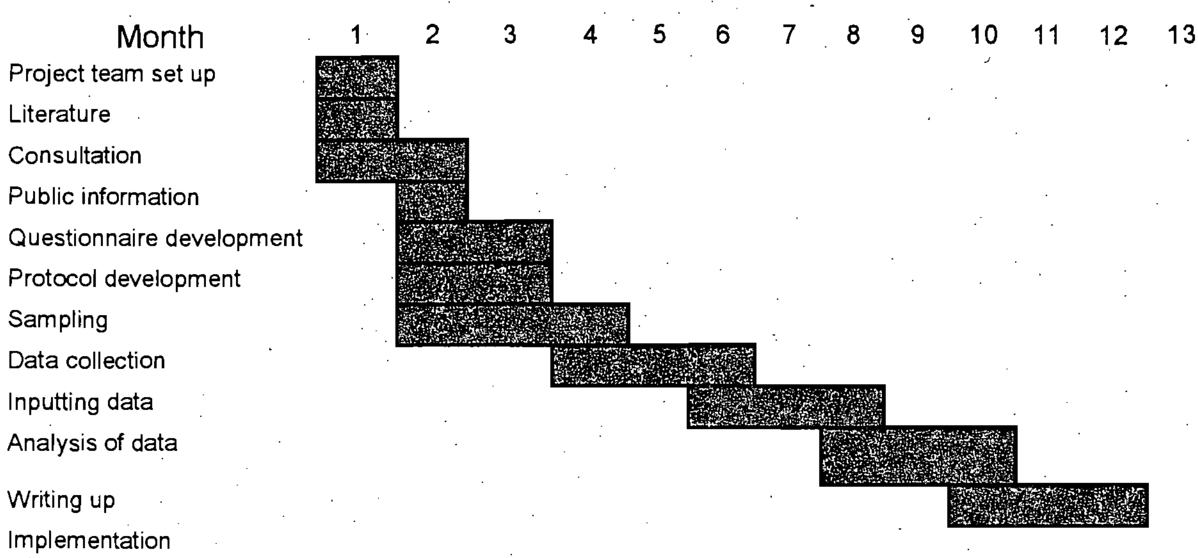
b) Genetic testing (*HFE* genotype)

DNA analyses will be carried out for the detection of both the C282Y and H63D mutations of the HFE gene.

**5.10** Inputting and analysis of the data will be performed by an the Department of Community Health and General Practice, Trinity College, Dublin

**5.11**
**5.12** } Publication of results and implementation of the recommendations

## 6 TIMESCALE



## COSTING

| | | |
|---|---|---|
| **Phlebotomy** | Bottles for 5000 patients<br><br>Test request forms | £3,000<br><br>£1,000 |
| **Staff** | Research Scientist | £27,000+PRSI=£30,375 |
| | Research Assistant Hospital lab | £18,000+PRSI=£20,250 |
| | Research Assistant Institute lab | £18,000+PRSI=£20,250 |
| | Project manager | £30,000+PRSI=£33,750 |
| | Nurse | £25,000+PRSI =£28,125 |
| | Geologist advice | £2,000 |
| | Travel | £20,000 |
| | Secretarial support | £6,000+PRSI=£6,750 |
| | Courier for samples | £2,000 |
| **Samples** | Water sampling 2,500 households | £5/sample=£12,500 |
| | Blood tests | £15/person=£75,000 |
| | Genetic testing | £45/person=£225,000 |
| **Administration** | Phone/stationery | £10,000 |
| | Publication and dissemination of results | £10,000 |
| **Equipment** | Nephalometer | £ 35,000+VAT=£42,000 |
| | PC for data collection and printer | £ 1,500+VAT=£1,800 |
| | Laptop computer and printer for field work | £3,000+VAT=£3,600 |
| | Freezer for lab for storage of samples | £2,000+VAT= £2,400 |

| | | |
|---|---|---|
| | Conductivity meters x4 | £2,800+VAT=£3,600 |
| | Lease of AA and analyser | £4,000 |
| | Chemicals and equipment | £4,500 |
| **Data Management** | Statistician | £3,600 |
| | | **<u>Total to date</u>** **£565,500** |

VAT calculated at a rate of 20%

PRSI calculated at a rate of 12.5%

# APPENDIX 1

## Project Steering Committee

Dr. Peter Wright, Specialist in Public Health Medicine, Dept. of Public Health, NWHB, Ballyshannon, Co.Donegal

Dr. Alan Kelly, Biostatistician Dept. of Community Health and General Practice, TCD, Tallaght Hospital, Dublin 24.

Dr. John Williams, Biochemistry Lab, Sligo General Hospital

Ms. Rita O'Grady, Principal Environmental Health Officer, NWHB, Sligo.

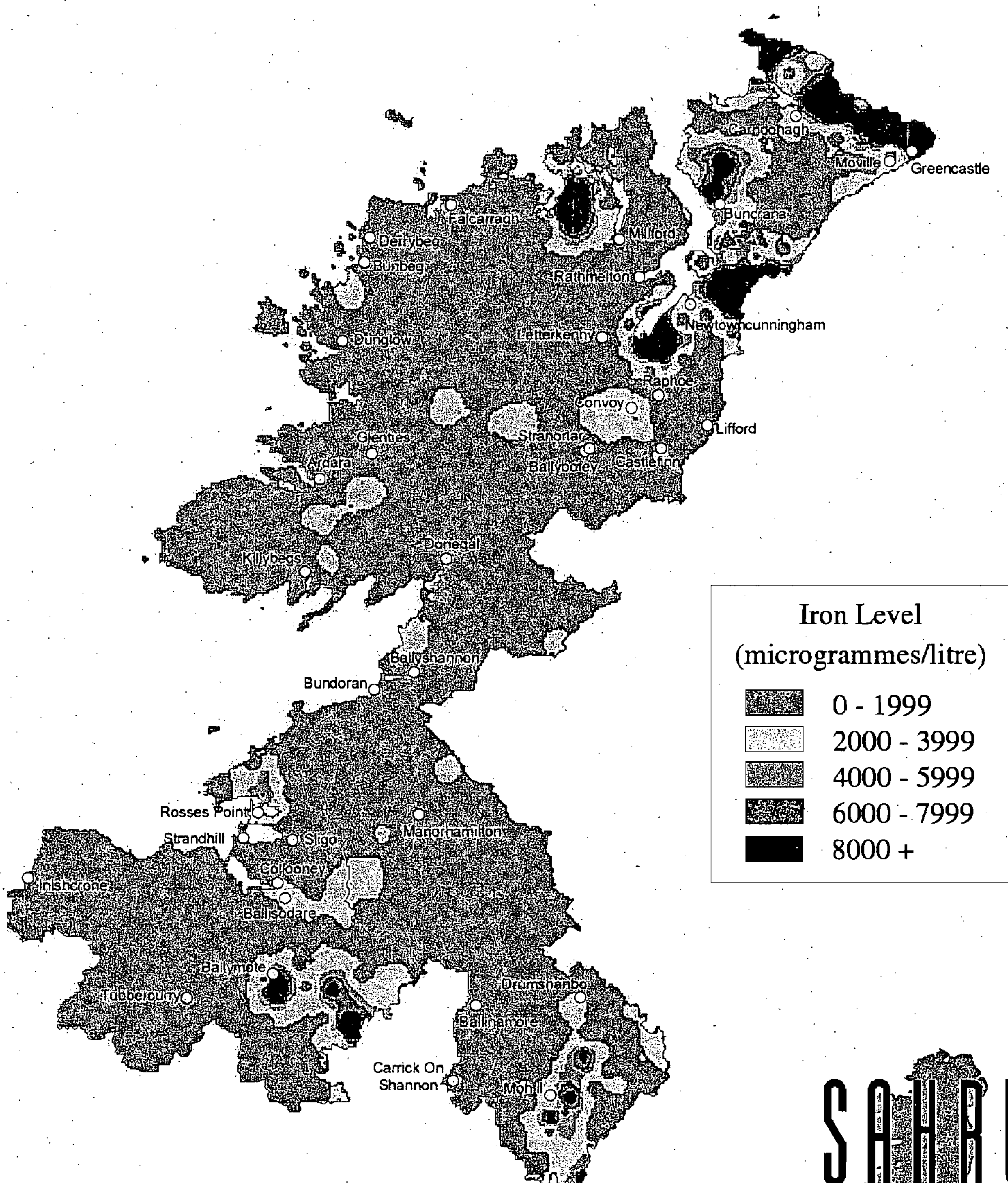
Dr. Louise Doherty, Specialist Registrar in Public Health, NWHB, Ballyshannon, Co. Donegal

Prof. Jim Houghton, Cytogenetics Dept., NUI, Galway

Mr Pat Timpson, Head of School of Science, Institute of Technology,Ballinode, Sligo

Representative from the Dept of Health (to be nominated)

# APPENDIX 2
# MAP

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# APPENDIX 3
# Geological Background

**Iron and Potable Water Sources**

## 1.0 SOURCES OF IRON

Iron is an extremely common metal and is found in large concentrations in soils and rocks, although normally in an insoluble form. However, due to a number of complex reactions which occur naturally in the ground, or which may be induced by organic pollution, soluble forms of iron can be formed which may then contaminate any water passing through the rock strata. Therefore, excess iron in groundwater is not an uncommon phenomenon.

Iron occurs in either the ferrous ($Fe^{++}$) oxidation state or as ferric ($Fe^{++}$) iron and may combine with a wide range of other elements and compounds to form various iron complexes. The type of iron found in a particular environment is primarily dependent upon the geology of the area, the redox potential and the pH of the environment. Broadly speaking , ferric iron is usually found in more oxidizing environments than ferrous iron, and both are more soluble in acid conditions.

Geologically, elevated concentrations of iron in groundwater are often associated with Old Red Sandstones, Namurian Sandstones and Shales. Many of the igneous rock-forming minerals have a high iron content and when these are attacked by water, particularly at low pH, the iron is released into solution. The Geological Survey of Ireland also indicated that iron problems may arise in muddy/impure limestones and lower Paleozoic and Precambrian rocks. It notes that the aquifer category is usually "poor" or "locally important", so transmissivities and specific capacities are usually low.

## Iron in groundwater

The relationships between the different iron compounds in water is extremelly complex and is affected by the source of the iron, Redox Potential and pH. Ferrous compound are relatively soluble in water but they oxidize rapidy at normal oxygen tension and form ferric compounds (normally hydroxides) which are very insoluble. At pH values greater than 8, the oxidation is extremely rapid but at pH values of less than 4, oxidation takes place more slowly and therefor, under these acidic conditions, the dissolved ferrous iron concentrations will be higher.

In summary, therefore, the oxidation/reduction of iron in groundwater plays a major role in determining the iron content of water and pH in turn, influences the rate of oxidation also the solubility of iron compound.

Groundwater in shallow wells normally has too high an oxidation potential to maintain iron in solution and the values are normally considerably less than the MAC value of 200 eg/L.

In confined aquifers, naturally occurring reducing conditions are common, particularly in low permeability rocks. This process is hastened in environments, where there is an abundance of reducing agents (eg pyritic shales) and such confined aquifers can produce water with elevated iron valued many times higher than the MAC. However, when water such as this is pumped to the surface and is oxidized, the iron will precipitate out as the hydroxide and typically give an orange sediment in the water tanks in a house.

## Groundwater mixing

Groundwater present in different horizons within an aquifer will often have different hydrochemical compositions. These horizons may be linked by faults in the natural environment, although the linkage may also occur via bored wells and as a result groundwater mixing will occur. In such an area, solutions of different redox potential and acidity are mixed together and compounds may become unstable as the equilibrating reactions occur.

This mixing of groundwaters from different horizons may explain the phenomenon of "high iron flushes". For example in meduom-deep wells, in a limestone environment, the mineral, which controls solution concentration of iron, is the carbonate, which is very soluble. In very deep wells, the iron is often in the form of a sulphide, which is very insoluble, but if such water from a deep well comes in contact with oxygenated water, with elevated bicarbonate values, iron carbonate, which is very soluble (rather than the iron hydroxide) may form and may therefore give rise to very elevated dissolved iron concentrations in the drinking water.

## Proposed Survey

A water sample will be collected, using recommended procedures, from each of the households included in the survey. The pH and conductivity will be measured on site and the water sample filtered and fixed, to maintain the iron in solution. The sample will be analysed for total dissolved iron.

It is clear form the above, that as groundwater conditions change, the water quality may also vary, particularly with the seasonal changes in groundwater levels. To investigate the potential seasonal variations in iron concentrations, it is proposed that at 10 households in each of the 5 survey areas water samples will be collected monthly for analyses over a one year period. On site measurement of pH and electrical conductivity will take place and in addition to the iron values, these samples will also be analysed for manganese, carbonates/bicarbonate and sulphate values. These parameters are particularly important in providing evidence of the mechanisms involved in elevated iron flushes.

# APPENDIX 4

## Water results from Sligo/Leitrim and Donegal

### LEITRIM PRIVATE WATER SUPPLIES 1990 - 1999

| Name of Scheme / Location | Chlorinated / Raw | Date of Sample | Iron in µg/l | Other parameters / Exceedences |
|---|---|---|---|---|
| **Carrigallen** | U.V. and Filtered | 20/4/98 | **2158** | Mn 68, Amm .4 |
| | | 2/6/99 | **7569** | Mn 178, Amm 1.81 |
| | | 10/12/97 | **9631** | Mn 327 |
| | | 6.4.98 | 842 | Amm .371 |
| | Raw | 7/4/97 | 471 | Mn 95 |
| | | 20/7/98 | 313 | Mn 205 |
| | | 25/2/98 | 1952 | Mn 34, Am 1.04 |
| | Sand Filtered | 22/6/98 | 249 | Am 1.33 |
| | Raw | 20/4/98 | 376 | |
| | | 20/1/98 | 371 | |
| | | 29/6/98 | 1840 | |
| | | 11/1/99 | 236 | |
| | | 18/5/98 | | Mn 55 |
| | Raw Filtered | 3/11/98 | 872 | Mn 432 |
| | Raw | 6/4/98 | 1578 | |
| | | 13/7/98 | | Mn 99 |
| | | 9/11/98 | | Mn 78 |
| | | 7/12/98 | | Mn 98 |
| | | 16/11/98 | 744 | Mn 30 |

| | | | | |
|---|---|---|---|---|
| | | 14/12/98 | 813 | Mn 70, Amm .4 |
| | | 26/6/99 | | Mn 116 |
| | | 26/6/99 | **4886** | Mn 115 |
| **Drumlish** | Raw | 2/3/98 | 947 | Mn 614 |
| | | 6/4/98 | 5126 | Mn 701,, Am .701 |
| | Raw Filtered | 22/6/98 | 20,040 | Mn 908 |
| | Raw | 20/9/99 | 1,100 | Mn 114 |
| **Glencar** | Raw | 11/2/98 | 269 | Mn 32 |
| | | 4/1/99 | 869 | Mn 142 |
| | | 27/9/99 | 6620 | Mn 717 |
| | | 18/8/97 | 16,860 | Mn 481, Am .8 |
| **Rossinver** | | 14/1/97 | 602 | Mn 52 |
| | | 11/3/98 | 294 | |
| | | 27/7/98 | 711 | |
| | | 14/12/98 | 9128 | |
| **Mohill** | | 18/7/98 | 1394 | Mn 404 |
| | | 6/7/98 | 223 | Mn 233 |
| | | 19/1/98 | 1280 | Mn 1200 |
| | | 6/7/98 | 2320 | Mn 84 |
| | | 20/1/98 | | Mn 568 |
| | | 25/11/97 | 2397 | Mn 191 |
| | | 22/6/98 | 3227 | Mn 543 |
| | | 31/8/98 | 2319 | Am .416 |
| | | 4/8/98 | 1436 | Mn 729 |
| | | 5/10/98 | 1740 | Mn 274 |
| | | 24/8/98 | 913 | Mn 396 |
| | | 29/11/98 | 1409 | Mn 319 |
| | | 2/3/98 | 9298 | Mn 144 |
| | | 2/6/99 | 1416 | Am .471 |
| | | 26/11/98 | 586 | |
| | | 25/1/98 | 2151 | Mn 228 |

| | | | | |
|---|---|---|---|---|
| | | 22/3/99 | 347 | Mn 283 |
| | | 30/8/99 | | Mn 381 |
| | | 25/3/99 | 334 | Mn 471 |
| | | 17/5/99 | 1902 | |
| **Bornacoola** | Raw | 31/8/98 | 14,730 | Mn 413 |
| | | 25/3/98 | 3,534 | Mn 156 |
| | | 3/11/98 | 253 | Mn 75 |
| | | 6/4/98 | 313 | |
| | | 20/4/98 | 3437 | Mn 85 |
| | | 21/11/97 | 2281 | Mn 67 |
| | | 28/9/99 | 239 | Mn 61 |
| | | 16/11/98 | 565 | Mn 59 |
| | | 14/12/98 | 2707 | |
| | | 22/2/99 | 570 | Mn 105 |
| | | 7/4/99 | 937 | Mn 69 |
| **Toomon** | | 17/5/99 | 7762 | Mn 235 |
| | | 5/10/98 | 4891 | Mn 55 |
| | | 25/3/98 | 3237 | Mn 60 |
| | | 18/8/98 | 718 | Mn 56 |
| | | 25/2/98 | 3733 | Am .72 |
| | | 2/3/98 | 7285 | Am 9.1 |
| | | 25/2/98 | 6539 | Mn 146 |
| **Newtowngore** | | 3/3/98 | 2334 | Mn 353 |
| | | 6/9/99 | 2076 | Mn 960, Am 0.678 |
| **Killygar** | | 24/8/98 | 4008 | |
| | | 13/5/99 | | Mn 173 |
| **Aughavey** | | 20/1/98 | 830 | |
| | | 10/12/97 | 8902 | Mn 163 |
| | | 12/10/98 | 1452 | Mn 217 |

| | | | | |
|---|---|---|---|---|
| | | 4/8/98 | 3202 | Mn 157 |
| | | 19/4/99 | 1490 | |
| | | 8/12/99 | 700 | |
| **Cloone** | Sandfilter | 7/12/98 | 8983 | Mn 360 |
| **Tawneymore** | Raw | 24/11/99 | 9824 | Mn 53 |
| **Dromahaire** | Raw | 4/11/99 | 396 | Mn 59 |
| | | 7/1/98 | 378 | Mn 124 |
| | | 18/11/98 | 5040 | Mn 444 |
| | | 11/2/99 | 2615 | Am 1.613 |
| | | 24/8/99 | 479 | Mn 184 |
| | | 27/9/99 | 15,650 | Mn 518 |
| | | 24/11/99 | 208 | Am 3.8 |
| **Dromard** | Raw | 3/2/98 | 1766 | Mn 161 |
| | | 31/8/98 | 2244 | Mn 89 |
| | | 26/11/98 | 1058 | Mn 89 |
| | | 28/6/99 | 691 | |
| **Lisclonadea** | | 13/7/98 | 11,370 | Mn 524 |
| | | 10/12/98 | 7493 | Mn 199 |
| **Drumgowna** | | 12/4/99 | 2739 | Mn 445 |
| **Ballinamore** | | 20/9/99 | 3560 | Mn 82 |
| **Dieter** | | 24/4/95 | 11,841 | Mn 1004 |
| **Rosses Point** | | 19/7/95 | 1935 | |
| | | 18/1/90 | 2500 | |
| | | 26/4/90 | 3750 | |
| | | 2/5/90 | 300 | |
| | | 8/8/90 | 450 | |
| | | 14/6/93 | 2496 | Mn 478 |
| | | 29/6/93 | 353 | Mn 108 |
| | | 2/9/93 | 272 | |
| | | 16/4/99 | 426 | |
| | | 4/6/96 | 860 | |

| | | | | |
|---|---|---|---|---|
| | | 9/9/99 | 1241 | 437 |
| | | 13/4/99 | 779 | 258 |
| **Mullaghmore** | | 19/7/95 | 740 | |
| | | 13/6/94 | 2724 | Mn 168 |
| | | 21/9/98 | 421 | |
| **Cartron / Killerdoo** | | 26/7/95 | 10,660 | Mn 288 |
| **Union Foods** | | 3/7/90 | 6250 | |
| **Springfield** | | 30/8/90 | 22,500 | Mn 1000 |
| **Drumcliffe** | | 10/9/90 | 1010 | |
| | | 8/6/94 | 3366 | |
| | | 9/3/99 | 1956 | |
| **Urlar** | | 23/5/90 | 7500 | |
| **Dunally** | | 5/6/90 | 6250 | Mn 116 |
| | | 18/1/94 | 3125 | Mn 357 |
| **Carney** | | 6/1/93 | 20,230 | Mn 548 |
| **Ballinafad** | | 16/3/93 | 13,360 | Mn 1757 |
| **Kilmacowen** | | 5/5/93 | 2615 | Mn 310 |
| **Drinaghan** | | 9/8/94 | 36,480 | |
| **Castlebaldwin** | | 19/10/94 | 9516 | Mn 331 |
| **Drumsinuagh** | | 12/96 | 2319 | Mn 919 |
| **Ballymote** | | 24/7/97 | 626 | Mn 73 |
| | | 20/10/98 | 37,950 | Mn 17,330 |
| **Ballisodare** | | 5/2/98 | 234 | |
| | | 12/5/98 | 3756 | Mn 64 |
| | | | | |

## Donegal Private Water Supplies 1990 – 1999

| Name of Scheme / Location | Chlorinated / Raw | Date of sample | Iron in µg/l | Manganese |
|---|---|---|---|---|
| Rosnowlagh | | 28/6/99 | 10,160 | 59 |
| Aughllin | | 18/10/99 | 10,000 | 989 |
| Townalagha | | 13/12/99 | 3743 | 722 |
| Pettigo | | 1/3/99 | 3002 | 705 |
| Rossnowlagh | | 28/6/99 | 2664 | 95 |
| Knocknashangan | | 7/9/98 | 1747 | 235 |
| Pettigo | | 1/3/99 | 1466 | 556 |
| Killybegs | | 23/8/99 | 1454 | 20 |
| Arbane | | 18/5/98 | 1428 | 1231 |
| Rossnowlagh | | 28/6/99 | 1404 | 178 |
| Bavin | | 12/4/99 | 1388 | 836 |
| Kilcar | | 16/8/99 | 1124 | 1705 |
| Bavin | | 19/4/99 | 1113 | 1193 |
| Carrick | | 26/7/99 | 875 | <20 |
| Pettigo | | 23/3/98 | 837 | 930 |
| Rossnowlagh | | 7/4/98 | 736 | 319 |
| Bundoran | | 21/6/99 | 702 | 59 |
| Ballintra | | 5/7/99 | 696 | 20 |
| Killybegs | | 2/7/99 | 679 | 20 |
| Drumlaght | | 23/9/99 | 667 | 20 |
| Pettigo | | 13/7/98 | 463 | 274 |
| Ballintra | | 12/12/99 | 207 | 1904 |
| Ardnawark | | 31/8/99 | 67 | 187 |
| Pettigo | | 18/10/99 | 57 | 48 |
| Kilraine | | 6/4/98 | 16,600 | 1330 |
| Ardara | | 24/8/98 | 12,020 | 576 |
| Monargan | | 31/8/98 | 6,034 | 425 |
| Banaghbuy | | 23/3/98 | 1055 | 636 |

| | | | | |
|---|---|---|---|---|
| **Ardara** | | 20/4/98 | 534 | 836 |
| **Fintown** | | 10/9/98 | 479 | <20 |
| **Monargan** | | 27/10/98 | 378 | <20 |
| **Kilraine** | | 18/8/99 | 231 | 34 |
| **Back Glen** | | 7/9/98 | 167 | 293 |
| **Fintown** | | 12/7/98 | 129 | 922 |
| **Malin Head** | | 20/9/99 | 50,490 | 1742 |
| **Moville** | | 25/5/98 | 37,400 | 104 |
| **Burt** | | 26/7/99 | 35,510 | 2097 |
| **Malin Head** | | 9/2/98 | 33,100 | 989 |
| **Bridgend** | | 13/9/99 | 31,700 | 937 |
| **Malin Head** | | 13/12/99 | 11,840 | 8543 |
| **Backhill** | | 5/1/98 | 10,560 | 128 |
| **Crockahenny** | | 12/5/98 | 10,370 | 735 |
| **Culdaff** | | 12/7/99 | 4136 | 931 |
| **Glengad** | | 21/11/98 | 4125 | 3300 |
| **Redcastle** | | 25/5/98 | 2950 | 930 |
| **Burnfoot** | | 23/8/99 | 2589 | 1049 |
| **Kinnego** | | 5/1/98 | 2509 | 2312 |
| **Carrobeg** | | 26/7/99 | 2203 | 446 |
| **Culdaff** | | 26/7/00 | 1981 | 920 |
| **Burt** | | 19/1/98 | 1382 | 91 |
| **Bridgend** | | 26/10/99 | 1364 | 984 |
| **The Illies** | | 18/1/99 | 1199 | 2651 |
| **Glenagivney** | | 15/2/99 | 1160 | 384 |
| **Glengad** | | 9/7/99 | 949 | 845 |
| **Ich Island** | | 9/3/98 | 921 | 739 |
| **Quigley's Point** | | 1/3/99 | 856 | 27 |
| **Buncrana** | | 21/6/99 | 781 | 22 |
| **Gortnaskea** | | 12/4/99 | 659 | 26 |
| **Gleneely** | | 25/5/98 | 516 | 45 |
| **Malin Head** | | 22/3/99 | 497 | <20 |
| **Malin Head** | | 9/2/98 | 477 | 312 |

| | | | | |
|---|---|---|---|---|
| **Moville** | | 5/7/99 | 434 | 21 |
| **Greencastle** | | 13/12/99 | 384 | 299 |
| **Ballinadavoe** | | 29/6/98 | 338 | 62 |
| **Linsfort** | | 16/7/99 | 254 | 732 |
| **Malin Head** | | 16/7/99 | 234 | 2108 |
| **Linsfort** | | 16/7/99 | 223 | 567 |
| **Redcastle** | | 11/10/98 | 162 | 769 |
| **Malin head** | | 24/8/98 | 102 | 1784 |
| **Linsfort** | | 24/5/99 | 98 | 42 |
| **Manorcunningham** | | 11/10/99 | 12,340 | 1504 |
| **Convoy** | | 17/8/98 | 8504 | 878 |
| **Castlefin** | | 16/6/98 | 3964 | 84 |
| **Trusk** | | 3/3/98 | 3802 | <20 |
| **Drumkeen** | | 1/3/99 | 3579 | 630 |
| **Convoy** | | 15/2/99 | 2707 | 1637 |
| **Glenmaquin** | | 17/5/99 | 1806 | 262 |
| | | 2/3/98 | 1580 | 196 |
| **Manorcunningham** | | 23/8/99 | 1392 | 78 |
| **Manorcunningham** | | 21/6/99 | 1193 | 5177 |
| **Raphoe** | | 21/9/98 | 1165 | 84 |
| **Manorcunningham** | | 23/3/98 | 1134 | 528 |
| **Convoy** | | 24/5/99 | 991 | 398 |
| **Raphoe** | | 21/6/99 | 812 | 172 |
| **Dromore** | | 18/5/98 | 774 | 70 |
| **Ballybofey** | | 6/4/98 | 747 | 20 |
| **Castlefin** | | 31/8/98 | 684 | 90 |
| **Convoy** | | 8/3/99 | 539 | 96 |
| **Lifford** | | 19/7/99 | 530 | 171 |
| **Glenmaguin** | | 27/9/99 | 492 | 72 |
| **Convoy** | | 12/4/99 | 369 | 526 |
| **Glenmaquin** | | 25/5/98 | 267 | 954 |
| **St. Johnston** | | 20/7/98 | 203 | 2608 |
| **Dooish** | | 19/4/99 | 184 | 2621 |

| | | | | |
|---|---|---|---|---|
| **Manorcunningham** | | 11/1/99 | 62 | 651 |
| **Convoy** | | 22/11/99 | 55 | 168 |
| **Drumnahoe** | | 14/9/98 | 50 | 3188 |
| **Glenvar** | | 21/9/98 | 50 | 741 |
| **Carnagore** | | 27/9/99 | 64,560 | 740 |
| **Carrigart** | | 8/11/99 | 35,310 | 2290 |
| **Glenvar** | | 17/8/98 | 21,670 | 683 |
| **Carrigart** | | 8/11/99 | 8866 | 1156 |
| **Carrigart** | | 21/6/99 | 7649 | 553 |
| **Carrigart** | | 8/11/99 | 5006 | 1251 |
| **Glenvar** | | 2/2/98 | 4389 | 6557 |
| **Carrigart** | | 25/5/98 | 3675 | 2949 |
| **Ballymagowan** | | 12/10/98 | 2632 | 460 |
| **Woodlands** | | 17/8/98 | 2266 | 1407 |
| **Ballymagowan** | | 2/11/98 | 2131 | 64 |
| **Carland** | | 20/9/99 | 2045 | 986 |
| **Golan** | | 8/11/99 | 2033 | 40 |
| **Gartan** | | 19/1/98 | 1166 | 154 |
| **Kerrykeel** | | 20/9/99 | 1142 | 23 |
| **Ramelton** | | 23/11/98 | 1100 | 245 |
| **Ramelton** | | 16/11/98 | 662 | <20 |
| **Churchill** | | 4/10/99 | 659 | <20 |
| **Downings** | | 20/4/98 | 608 | 106 |
| **Cranford** | | 11/5/98 | 591 | 376 |
| **Rathmullan** | | 29/11/99 | 524 | 210 |
| **Rann** | | 8/6/99 | 518 | <20 |
| **Dundoan** | | 27/9/99 | 334 | 786 |
| **Downings** | | 10/5/99 | 194 | 473 |
| **Downings** | | 2/3/98 | 190 | 712 |
| **Downings** | | 1/3/99 | 167 | 399 |

# APPENDIX 5

## Literature Review

Hereditary hemochromatosis is an autosomal recessive condition, characterised by excessive absorption of dietary iron that can lead to progressive iron accumulation in tissues and organ damage.[1] In 1996 a gene for hereditary hemochromatosis was discovered , *HFE,* along with two mutations (C282Y and H63D).[2] Hereditary hemochromatosis affects one in eight of the European population who are carriers of the single gene (heterozygotes). Homozygous C282Y affects about 1:250 of all white populations.[3] It is particularly prevalent in those of Celtic descent with a 10-14% allele frequency for C282Y reported in the chromosomes of a normal Irish population.[45] The clinical penetrance of this gene is unknown. In one study only half of those who were homozygous had clinical features of hemochromatosis and one quarter had serum ferritin levels that remained normal over a four year period.[6]

Hemochromatosis can also be acquired, as opposed to genetic, resulting from repeated blood transfusions, massive excess of dietary iron, or rare metabolic disorders such as porphyria cutanea tarda and atransferrinemia[7] Excessive oral iron intake may lead to secondary hemochromatosis even in HFE C282Y negative subjects.[8] Increased dietary iron predisposes to the condition of African iron overload[9]. Excess dietary iron is derived from a traditional beverage that contains alcohol.

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[1] Witte D.L., Crosby W.H., Edwards C.Q., Fairbanks V.F., Mitros F.A. Practice guideline development task force of the college of American Pathologists. Hemochromatosis. Clin Chim Acta. 1996;245:139-200

[2] FederJ.N., Gnirke A., Thomas W. et al. A novel MHC class 1-like gene is mutated in patients with hereditary haemochromatosis. Natural Genetics 1996;13:399-408

[3] Allen K., Williamson R. Screening for Hereditary Haemochromatosis should be implemented now. BMJ 2000;320:183

[4] Lucotte G. Celtic origin of the C282Y mutation of haemochromatosis. Blood Cells Mol Dis 1998; Oct 31:433-8

[5] Ryan E., O'Keane C., Crowe J. Hemochromatosis in Ireland and HFE. Blood Cells Mol Dis 1998 Dec;24(4)428-32

[6] Olynyk JK, Cullen DJ. Aquilia S. et al. A population based study of the clinical expression of the haemochromatosis gene. N Engl J Med 1999 Sep 2;341(10)718-24

[7] Edwards CQ., Griffen LM., Kushner JP. Disorders of excess iron. In Herber V1980 Diagnosis and treatment of Iron Disorders. Hospital Practice;26(Suppl 3 April):30-36

[8] Bell H., Berg JP., Undlien DE et al. The clinical expression of haemochromatosis in Oslo, Norway. Excessice iron inatake may lead to secondary haemochromatosis even in HFE C282Y mutation negative subjects. Scand J Gastroenterol 2000 Dec;35(12):1301-7

[9] Kasvosve I., Gangaidzo IT., Gomo ZA., Gordeuk VR. African iron overload. Acta Clin Belg 2000 Mar-Apr;55(2):88-93

Iron and/or vitamin C supplementation enhance iron absorption and worsen iron overload[10]. Dietary iron supplementation of food was begun in the USA in 1940 and in Denmark in 1954. In the USA there was no strong evidence of an increase in hemochromatosis from mortality, morbidity, or health survey data which implies that the iron supplementation did not accelerate manifestations of hemochromatosis.[11] In Denmark iron fortification of food was abolished in 1987 and subsequent studies showed no apparent negative effect on iron status in men.[12]

With a valid genetic test, it is possible to identify persons with hereditary hemochromatosis even before abnormal serum iron status is detectable and to follow them carefully so that treatment can begin before iron accumulation occurs.[13] Furthermore, an effective treatment (repeated phlebotomy) is readily available, low risk and not overly costly. Early diagnosis[2] and venesection restores normal life expectancy and usually some improvement in symptoms.[14]

It has not been possible to identify population studies on areas with high levels of iron in drinking water.

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[10] Cooke [10] Niederau C., Fischer R., Purschell A. et al. Long Term Survival in patients with hereditary hemochromatosis. Gastroenterology 1996;110:1107-1119JD., Monsen ER. Vitamin C, the common cold and iron absorbtion. Am J Clin Nutr.1997;30:235-241

[11] Gable CB. Hemochromatosis and dietary iron supplementation:implications from US mortality, morbidity, and health survey data. J Am Diet Assoc 1992 Feb;92(2):208-12

[12] Milman N., Ovesen L. et al. Iron status in Danes updated 1994. I: prevalence of iron deficiency and iron overload in 1332 men aged 40-70yrs. Influence of blood donation, alcohol intake and iron supplementation.

[13] Franks A.L., Marks J.S. Introduction to Supplement on Iron Overload, Public Health, and Genetics. Ann Int Med 1998 129:923-924

[14] Niederau C., Fischer R., Purschell A. et al. Long Term Survival in patients with hereditary hemochromatosis. Gastroenterology 1996;110:1107-1119