REPORT ON THE SUPPLY AND DEMAND OF 18O ENRICHED WATER

AD HOC COMMITTEE OF THE NORTH AMERICAN SOCIETY FOR THE STUDY OF OBESITY,
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1. Statement of the Problem

Oxygen-18 is a stable isotope that is used as a tracer for several biomedical applications. The two primary applications are the study of organismal energy expenditure and organ specific utilization of glucose. The former uses ^{18}O along with deuterium to measure carbon dioxide production of free-living animals and humans. Total energy expenditure is calculated from carbon dioxide production using the standard equations of indirect calorimetry. The later uses ^{18}O as a precursor for the production of ^{18}F, a radionuclide that is incorporated into glucose homologues and injected into the circulating blood. When the glucose homologues are taken up by an organ (usually brain), the organ can be imaged using positron emission tomography (PET).

Both of these techniques have become major research and, in the case of PET, diagnostic tools during the last decade. This growth in the use of these tools has increased the world-wide demand for ^{18}O in the form of water. In 1998, this demand could not be met by suppliers and significant delivery delays have been encountered by many investigators and clinicians. Some suppliers are quoting delivery delays of a year. These delays have disrupted on-going research and delayed the start of new projects. The shortage has resulted in a price increase of nearly 50% in ^{18}O water.

The disruption of ^{18}O supply in 1998 is the second such disruption in the past decade. Commercial suppliers could not provide sufficient product in late 1990 following the forced closure of the US government production facility at Los Alamos Laboratory. Delivery delays lasted throughout 1991.

In August of 1998, the council of the North American Association for the Study of Obesity formed an ad hoc committee to gather information regarding the supply and demand for ^{18}O and to investigate potential solutions to the problem. The committee was chaired by Dale A Schoeller (University of Wisconsin). Members included James DeLany (Pennington Center), Van Hubbard (NIDDK), Peter Jones (McGill University), and Klaas Westerterp (Maastricht University, IASO member). In addition there were three consultants: Andrew Coward (IAEA), Gerald Kuhs (Institute for Clinical PET), and Richard Troiano (NCI).

2. Demand for 10 Atom Percent ^{18}O Water

The demand for 10% ^{18}O is almost exclusively dictated by its use for measurement of total energy expenditure by the doubly labelled water method. Of this usage, the vast majority is used by those measuring human energy expenditure. To estimate world demand for 10% ^{18}O, we assembled a list of investigators who have published papers in which the doubly labelled water method was used, or who have recently received grant funding for a doubly labelled water study. Individuals on this list were contacted and ask to report how much ^{18}O they used in 1997 and 1998 and to project usage for 1999 and 2000. To this total, we added 5 kg for the use by the wildlife ecologists and comparative zoologists for animal studies. There were 52 investigators from 10 countries in North America and Europe. The response rate was 79% and it included all the major isotope ratio mass spectrometry centres so it is unlikely that a major user did not report. Use was expressed as kg of 10 atom percent water. The equivalent weight of 95% atom percent water is given in parentheses. Number of doubly labelled water studies was estimated assuming 90 g used each adult study, 40 g for a paediatric study and a 70/30 split between adult and paediatric studies.

1997	142 kg (15 kg)	1900 studies
1998	171 kg (18 kg)	2300 studies
1999	306 kg (32 kg)	4100 studies
2000	237 kg (25 kg)	3200 studies

The number of non-responders should not add dramatically to the total use because they are not associated with major isotope ratio mass spectrometry centres and thus are limited in terms of analytical throughput. They may increase utilization, but the increment should not exceed 10%. No adjustment is made in our estimates for this factor, because we believe the information provided to us by responders probably overestimates usage slightly.

3. Demand for 95+ Atom Percent ^{18}O Water

In a 1997 marketing report, Frost and Sullivan estimated the number of PET studies using ^{18}F FDG to increase at the following rate:

1998	70,000 scans
1999	140,000 scans
2000	310,000 scans
2001	650,000 scans

These numbers are based on the proliferation of dual purpose PET/SPECT imaging scanners and reimbursement approval of PET scans by Medicare.

Each "batch" of FDG produced uses one or more target irradiations of ^{18}O water to produce ^{18}F for the FDG synthesis. Each FDG synthesis produces enough FDG for one or more doses. The variables that must be considered are: the quantity of ^{18}O water in the target load, the duration of irradiation, (hence the amount of ^{18}F produced), the percentage yield of the FDG synthesis, and the proximity of the patients to the FDG production site (decay in transit). It is our best estimate that currently each patient dose produced uses approximately 0.33 gm of ^{18}O water. As the number scanners increase and the proximity of patients to the production site decrease, the number of doses per batch of FDG produced should increase. In our estimation the number of grams of ^{18}O water per patient dose should decrease on the following schedule: 1999, 0.25 gm/dose; 2000, 0.2 gm/dose; 2001, 0.15 gm/dose.

Multiplying the number of estimated scans by the amount of ^{18}O water per scan produces the following estimated need for ^{18}O water in the US:

1998	70,000 x 0.33 gm	23.1 Kg
1999	140,000 x 0.25 gm	35.0 Kg
2000	310,000 x 0.20 gm	62.0 Kg
2001	650,000 x 0.15 gm	97.5 Kg

As the demand increases, it is our belief that a number of facilities will begin to recover the irradiated ^{18}O water after removing the ^{18}F produced with an ion exchange column. Using current technology, it is possible to recover, re-distill, and re-irradiate recovered ^{16}O water at least once without further isotopic enrichment. We believe that this process will diminish the demand for ^{18}O water by 25% in 1999, 35 % in 2000, and 50 % in 2001. Recovery and reprocessing will result in the following adjusted U.S. demand:

1998	23.1 Kg
1999	26.3 Kg
2000	40.3 Kg
2001	48.8 Kg

We were not able to gather usage information for PET outside of the U.S. Data that was collected for the use of 10% ^{18}O, however, indicated that the U.S. usage accounted for 89% of the world-wide market. If this same factor is applied to PET demand, then the adjusted world-wide usage increases. In addition, other uses such as synthesis of tracers other than water a guessed to require an addition 2 kg each year. Total world-wide, adjusted 95+% ^{18}O water demand is estimated to be:

1998	28 kg
1999	32 kg
2000	47 kg
2001	57 kg

4. Combined ^{18}O Demand

The total world-wide demand for ^{18}O is estimated from the sum of uses for ^{18}O water at 10% and 95% enrichments. PET usage for 1997 was not available, but a figure of 15 kg was estimated by back extrapolation of number of scans (1997=35,000) and per scan ^{18}O use (1997=0.41 gm). The use of 10% ^{18}O for 2001 was not collected, but usage is estimated as the average of the projections for 1999 and 2000. The results are expressed as kg of 95% ^{18}O water.

1997	31 kg
1998	46 kg
1999	64 kg
2000	72 kg
2001	86 kg

5. Production Capacity

There are four commercial ^{18}O producers in the world. These are, in alphabetical order, Cambridge Isotope Labs (U.S.), Isonics (Russia), Isotec (U.S.) and ROTEM (Israel). The capacity of these producers is not directly available. These producers isolate ^{18}O by distillation of water or nitrous oxide using large, steady state distillation columns. The production capacity can be estimated from the number and types of columns. For 1997, the world-wide production capacity of 95+% ^{18}O water was estimated to be 35 kg.

The production capacity for 1998 was estimated to decrease. This resulted from a temporary shut down on the part of one of the major producers during a move to a new production facility, and temporary reduction in sellable product as another producer directed a portion of their production to bring a new distillation column on-line in 1999. The estimated production for 1998 was reduced to 20 kg.

Increases in production capacity for 1999 are predicted. This includes a return to 1997 levels of production for the extent columns. In addition, the producers have additional columns under construction. These new columns are expected to come on-line during 1999 and 2000. Production capacity, expressed as 95+% ^{18}O water for the period 1997-2001 is estimated as:

1997	35 kg
1998	20 kg
1999	65 kg
2000	85 kg
2001	100 kg

6. Production Shortfall and Potential Solutions

Comparison of the usage and production estimates indicates that there is a shortage of about 22 kg of 95+% equivalent ^{18}O water. While this may have been buffered by producer's inventories and materials already in the hands of end users, the shortage became acute in first half of 1998. While supply is estimated to meet demand for 1999, estimated production capacity of 1999 is not sufficient to eliminate the backlogged demand until 2000, unless additional steps are taken. One potential solution would be to put more production columns on-line. Unfortunately, this is not an immediate solution. A new column requires an investment of $3-5 million, 9-12 months to build plus 6-9 months to bring to equilibrium before production of the specified ^{18}O enriched product. It might be possible to speed up this process if a currently unused column is brought into production. This would reduce cost and construction delays. Although the exact location and condition of such columns is unknown at this time, members of the committee are aware that the Russian (Georgian?) plant is not producing at full capacity. The reason for this is unknown, but it is assumed to be related to a combination of shortage of capitol for repair/upgrade, loss of workers following the civil disturbances of the early 1990s, and transportation problems. Three other producers have gone out of production and the fate of their columns is unknown. These include a ^{13}C production unit at PROCHEM (U.K.), an ^{18}O distillation unit at Los Alamos Labs (U.S.), and a water distillation unit in Karlsruhe (Germany). The columns at PROCHEM and Los Alamos were generally believed to have been old and may well have been scraped. The Karlsruhe unit may have been sold to British Oxygen and later to a U.S. company.

Another potential short term solution is recovery of excess ^{18}O from other isotopic production. The production of ^{13}C generally involves distillation of carbon dioxide. The resulting $^{13}CO_2$ is also enriched in ^{18}O. This might be recovered by reduction to methane and water, but the $^{13}CH_4$ must be re-oxidized before it is useful for synthesis of ^{13}C labelled compounds. The ^{18}O might also be partially recovered by equilibration with water, but this would severely reduce the ^{18}O enrichment. Production of deuterium by water distillation also enriches the ^{18}O, but this too is generally a low enrichment product. Neither method is cost effective at 1997 prices, but might be cost effective at current prices. The enrichments are low and cannot meet the needs of PET users, but most doubly labelled water users can use 5 atom percent water and some can even use 3 atom percent $1^{18}O$ water. It is a curious observation that until the mid-1980s, ^{18}O was a by-product of ^{15}N production and generally went unsold.

Alternate production methods should be explored given the growing market for ^{18}O and the cost limitation of distillation. Although still distillation based, one alternative might be to construct an O_2 distillation unit. This should be less costly to build and run that current nitrous oxide or water distillation units, but it could only produce low enrichment water for use by the doubly labelled water community. A diffusion based system of enriching water has been said to be effective (DISOTEK, http://www.incubators.org.il/27008.htm), but attempts to contact the company have failed. Other technologies such as laser based separations may offer low cost alternatives to distillation. It should be noted that NIH has included the development of new technologies for ^{18}O production among its request for proposals for the small business grant program.

A final potential solution that is of particular interest, because it could be implemented in the shortest time and thus eliminate the shortage during 1999, is recycling of the used ^{18}O water from PET facilities. During use for PET, the water becomes contaminated with heavy metals sputtered from target and becomes diluted. The metals can be removed by ion exchange chromatography, but the dilution limits the utility for PET because ^{16}O yields products that interfere with the ^{18}F imaging. It should be noted that the ^{18}F contamination is of little concern because the half-life is less than 2 h. As such, the radioactive ^{18}F is reduced by a factor of more than 8000 every 24 h. The recycled ^{18}O water would be of use for low enrichment applications including doubly labelled water and some of the PET applications. The limitation for doubly labelled water use would be an assurance of purity so that it could be ingested by humans. EPA specifications for drinking water purity are published on their web site (http://www.epa.gov/OGWDW), although human use committees might well request a further reduction with regard to the presence of radionuclides. An assurance of radionuclides concentrations at or below the 1-5 picocurrie/L range, which would be less than EPA standards, might eliminate any such concern.

7. Additional considerations

There are several variables that were not considered in this report. One is that investigators might abandon current research during the present shortage and redirect their efforts to projects that do not require ^{18}O. This is has occurred during 1998, but it is not clear if the trend will continue as supply improves. Indeed, only one investigator indicated that the ^{18}O shortage had caused him to abandon future planned studies indicating that a significant shift in investigator focus is unlikely. We also did not consider the potential increase in demand that might accompany increased funding from NIH. It is not unreasonable to conclude that demand will grow an additional 10% each year if NIH funding increases by 10%. Based on similar reasoning, however, the 50% increase in cost may reduce usage and cancel the effect of increased NIH funding. Lastly, in making our production projections, we made no attempt to estimate the likelihood of plant failures that might reduce production on a temporary basis. All of these factors are difficult to include in the production and demand estimates. The effect, however, is likely to lead to a modest increase in demand and decrease in production. The exception to this would be increased production resulting from additional investments in new production facilities, which would increase production beyond the estimates made in this report.