Appendix 5
Calculation of Estimated Creatinine Clearance (CrCl)

Many drugs used in the treatment of cancer patients are excreted by the kidney (carboplatin, methotrexate etc). For some drugs the kidney may be the only or major route of excretion. Abnormalities in renal function may therefore reduce the excretion of a drug, leading to higher drug levels for longer periods of time and therefore an increase in toxicity. Also, for drugs that are predominantly excreted by the kidney, very good renal function may lead to relatively lower drug levels and even a decrease in the effectiveness of the drug.

It is therefore important in many instances to assess the renal clearance of a drug, so that doses can be reduced in the presence of renal dysfunction to prevent unacceptable toxicity, or to tailor the dose of a drug to the patient's renal function (e.g. carboplatin)

There are a number of ways of estimating this, all based upon measurement of the Glomerular Filtration Rate (GFR). GFR is the standard indicator of renal function. Normal values are 120-130mls/min. GFR levels decline with increasing age.

a) Directly Measuring the GFR

GFR can be measured directly by calculating the renal clearance of a marker such as Inulin (freely cleared by the kidney) or a radiolabeled assay (CrEDTA, Iothalamate, 99TCDTPA), the compounds are administered intravenously and then the amount excreted by the kidneys in a given time is calculated. These tests are not routinely performed in clinical practice in Canada due to cost and inconvenience. Instead, creatinine levels can be used to estimate or measure GFR.

These methods are not ideal, as serum creatinine levels can be affected by drugs, ingestion of large amounts of meat, and changes in muscle mass. The estimation of creatinine excretion by 24-hr urine collection also depends on the adequacy and accuracy of the collection. Nonetheless, they represent a practical, if somewhat crude method of assessing renal function and GFR.

b) Estimating GFR by Measuring Endogenous Creatinine Clearance

Endogenous Creatinine Clearance can be measured by taking a serum creatinine sample and then collecting a 24 hour urine sample to measure total creatinine excreted over that period. The clearance can then be easily estimated.

$$CrCl=(UrineCreatinine \times UrineVolume)/(1440 \times SerumCreatinine)$$

Serum Creatinine measured in mg/dL
Urine Creatinine measured in mg/dL
Urine Volume measured in mL/24 hrs

(Comstock,TJ. Pharmaco Therapy; Elsevier 1992:645-659)

This is usually a reasonable estimation of GFR except in patients with significant renal dysfunction, where Creatinine Clearance overestimates true GFR by up to 50%, because of an increasing contribution of tubular secretion of creatinine. This is usually a reasonable estimation of GFR except in patients with significant renal dysfunction, where Creatinine Clearance overestimates true GFR by up to 50%, because of an increasing contribution of tubular secretion of creatinine.

c) Estimating GFR by Calculating Creatinine Clearance

Creatinine Clearance can be calculated from serum creatinine values by one of two formulas: Cockroft and Gault or the Jelliffe Method. Computerized order entry systems such as CCO's OPIS/2000 program will calculate the GFR (or Creatinine clearance-CrCl) once the ordering physician enters a serum creatinine value. A measured GFR(CrCl) may also be entered.

Cockroft and Gault (from Nephron 1976;16:31-41)

$$\text{i)} \qquad CrCl\ (mL/min) = \frac{[(140\text{-age}) \times weight]}{72 \times Cr}$$

- where age is in years, weight is in kg, and Cr is in mg/dL.
- in females, the result is multiplied by 0.85

In order to use SI units for creatinine (µmol/L), the following formula may be used:

$$\text{ii)} \qquad CrCl\ (mL/min) = \frac{[(140\text{-age}) \times weight]}{Cr} \times 1.23$$

- in females, the result is multiplied by 0.85 as above

Jelliffe Method (from Ann Int Med 1973;79:604-605)

$$\text{iii)} \qquad CrCl\ (mL/min) = \frac{[98 - (0.8 \times (age\text{-}20))]}{Cr}$$

- where age is in years to the nearest decade
- in females, the result is multiplied by 0.9

Important Notes

1. The above formulas (except ii) used to calculate Creatinine Clearance are based on U.S. units, but the values supplied by most Canadian labs are in SI units. Prior to calculating the GFR or the carboplatin dose, the following calculations must be made to convert the serum creatinine and creatinine clearance values from SI units to U.S. units:

	U.S.	SI(Can.)	U.S. $\rightarrow$ SI	SI $\rightarrow$ U.S.
Cr	mg/dL	μmol/L	x 88.4	x 0.0113
CrCl	mL/min	mL/s	x 0.0167	x 59.9

2. For reference, normal values for serum creatinine range from 70-120 μmol/L and Creatinine clearance (CrCl) values range from 1.24-2.24 mL/second.

Calculating Drug Dosages according to GFR

The emerging standard for calculation of carboplatin therapy dosage is to base the dose on creatinine clearance as a surrogate for carboplatin clearance. The most commonly used formula was developed by Dr. Calvert and is referred to as the "Calvert Formula". Although this formula is currently being used for carboplatin dose calculations, it appears that an increasing number of new drugs being developed are using the same sort of formula. The formula is as follows:

Carboplatin dose (mg)=AUC x [GFR or CrCl† (mL/min) + 25]

- Where **AUC** is the Area Under Curve (mg/mL/min), which is supplied in the regimen by the oncologist, and
- **GFR** is the Glomerular Filtration Rate (mL/min).

Calvert AH, et al. J Clin Oncol 1989; 7:1748-1756.

†**Note**: Older methods overestimated low levels of creatinine. Serum creatinine measured by the Isotope Diluted Mass Spectrometry (IDMS) method accurately measures creatinine, producing potentially lower levels than would have been reported with older methods; thus the lower limits of normal are significantly lower than the limits in the past. Using the IDMS method, if the creatinine levels are low, the calculated creatinine clearance (CrCl) and the estimated GFR may be substantially <u>higher</u> than the normal GFR when formally measured using radioisotopic methods. The Calvert formula was developed using the older methodology and using it uncapped may result in certain patients with low serum creatinine levels appearing to have a very high GFR, and thus receiving very high and inappropriate doses of carboplatin with resulting toxicity.

To avoid toxicity, FDA recommends capping the carboplatin dose for a desired AUC. The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function:

Maximum Carboplatin Dose (mg) = target AUC (mg/mL per min) x (125 mL/min + 25)

Chatelut has derived a more accurate formula for directly **calculating carboplatin clearance** (JNCI 1995;87(8):573-579).

The Chatelut formula may be used to estimate carboplatin clearance, but not GFR. Prospectively, this formula predicted the carboplatin clearance with good precision and minimal bias and was as accurate as the method of measurement of glomerular filtration rate following the injection of 51 chromium-EDTA. The formula is as follows:

$$Cl_{carboplatin} \ (ml/min) = 0.134 \times weight + \frac{[218 \times weight \times (1 - 0.00457 \times age) \times (1 - 0.314 \times sex)]}{Creatinine \ (\mu mol/L)}$$

- Weight is in kg.
- Age is in years
  Sex=0 if male, sex=1 if female

Calvert has also published further on this methodology as reported in Seminars in Oncology 1999;26(1):90-94.

Dec 2010: Added FDA CrCl cap and removed usual GFR value.