RECYCLED WATER QUALITY

A guide to determining, monitoring and achieving safe concentrations of chemicals in recycled water

Review prepared for the Environment Protection and Heritage Council (EPHC),
the National Water Commission and the Queensland Government
by the National Research Centre for Environmental Toxicology
(ENTOX), TOXIKOS and the University of New South Wales

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A guide to determining, monitoring and achieving safe concentrations of chemicals in recycled water

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Signed for and on behalf of UniQuest Pty Limited

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REVIEW PREPARED FOR ENVIRONMENT PROTECTION AND HERITAGE COUNCIL (EPHC), THE NATIONAL WATER COMMISSION AND THE QUEENSLAND GOVERNMENT

BY THE NATIONAL RESEARCH CENTRE FOR ENVIRONMENTAL TOXICOLOGY (ENTOX), TOXIKOS AND THE UNIVERSITY OF NEW SOUTH WALES

May 2008

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Executive Summary

Section 1 Introduction

The purpose of this project was to investigate scientifically justified human-based chemical quality guidelines for recycled water uses that lead to human exposure. The water sources that are relevant to this review include water from sewage treatment plants, water mining from sewers and managed aquifer recharge. In addition, it was requested that the document recommend appropriate source control and treatment technologies to reliably reduce concentrations of chemical contaminants, and options (if any exist) for public health surveillance to detect impacts to human health from exposure to these chemicals.

The information in this report is intended to

- provide input to the Joint Steering Committee for the National Guidelines for Water Recycling on Phase 2 of the guidelines which includes providing guidance on the use of recycled water for drinking water source augmentation
- provide a consistent and authoritative review of chemical hazards in recycled water to State and Territory governments that may be considering regulation of water recycling schemes involving a range of uses.

This report considers the greatest potential exposure to recycled water (by augmenting drinking water supplies) as the worst case scenario. Exposure due to irrigation of crops and industrial exposures are expected to be substantially less than through drinking water. Therefore, the guidelines proposed for drinking are expected to be protective of human health for all other recycled water applications as well.

Questions or tasks identified by the project brief included

- What are the chemicals of concern including mixtures and breakdown products? (Section 2)
- What are the acceptable safe levels of human exposure to these chemicals? (Section 2)
- What are appropriate margins of safety for these chemicals? (Section 2)
- What are the best methods to reduce or remove these chemicals from source water? (Section 3)
- What is the efficacy and reliability of specific recycled water treatment technologies to reduce chemical contaminants? (Section 3)
- What are the most practical means for monitoring these chemical contaminants (or their potential health effects)? (Section 4)
- Make recommendations on the feasibility and design of public surveillance and/or epidemiology studies? (Section 5)
- To assist with the communication of the outcomes of the project by providing data on comparative risk from exposure to chemicals from sources other than water. (Section 5).

Section 2 Setting guidelines for chemicals in drinking water augmented with recycled water

This section of the report explains the process for setting guidelines to protect human health from chemicals in drinking water when recycled water is used as a source. Throughout this chapter, the term drinking water guideline (DWG) refers to a concentration of chemical in drinking water delivered to the consumer that may include recycled water. In other words, if the water complies with the Australian Drinking Water Guidelines or World Health Organisation Guidelines, then

drinking water augmented with recycled water is safe to drink. Essentially the DWG is the concentration of a chemical in drinking water that is without harm should the water be drunk over a life time. The drinking water guidelines recommended here for chemicals have human consumers as the target. The overriding philosophy applied in this document is that drinking water produced from source water that may contain recycled water should be at least as safe as that from traditional raw water sources. Consequently, the recommended guidelines have been established in a way that is consistent with approaches currently used in Australia and internationally for setting health protective guidelines for chemicals potentially found in food, water and/or air.

The main focus of this chapter is the process for setting guidelines for chemicals for which no drinking water guideline is available. This is achieved as outlined in the decision tree (Figure 2.1) and the text describes the process for setting guidelines for chemicals in recycled water that will be augmented into drinking water supplies. The data set that was established for this purpose includes chemicals identified in secondary sewage effluent in Australia (Table 2-1) and those identified in data sourced from overseas reuse schemes (Table 2-2). A list of chemicals screened for, but not found at the time of data collection (early 2007), appears as an Appendix in the draft guidelines (EPHC 2007). Table 2-3 provides recommended drinking water guidelines established from toxicological information, or agency derived no observed effect concentrations (NOELs; Table 2-4).

For chemicals for which there is not a guideline, or for which reliable toxicological information is not available, a threshold of toxicological concern (TTC) approach has been used (Tables 2-7 to 2-9). The TTC approach has not been applied for pharmaceuticals; because the biological activity (ie. the therapeutic effect) for pharmaceuticals is well defined it is unusual for TDIs to be established for these pharmaceuticals with the exception of agricultural and veterinary purposes. The approach adopted to derive a guideline for pharmaceuticals was to divide the lowest therapeutic dose (as mg/kg/day) by safety factors.

The recommendations for each of these methods has been consolidated and presented in summary in Table 2-11.

Section 3 Source control and efficacy of treatment

Mitigating the risk posed by chemical contaminants can be achieved by: limiting the amount of contaminants entering the wastewater stream (source control), or ensuring their proper removal from the wastewater prior to discharge or use as source water for advanced treatment. If a point source can be identified then there is potential for control at the source of contamination for particular chemicals. Control of trade and industrial waste is also necessary to protect the operation and performance of the wastewater treatment plants as well as any downstream effects that may result from less than optimal removal. Section 3 of this document discusses the sources of groups of chemicals, presents an overview of some Australian source control programs and a case study from the Orange County Sanitation District.

The application of dedicated treatment process in a series of multiple barriers is the most effective way to attenuate chemical contaminants and mitigate the risk of exposure. The efficacy of individual treatment barriers can range from less than 90% removal to more than 99.99% removal depending on the nature of the chemical and the removal mechanisms (treatment technologies). Removal mechanisms include adsorption (at solid-liquid interfaces), size exclusion or reduced diffusion (across semi-permeable membranes); photolysis (exposure to UV light), and oxidation (in the presence of free radical or photo-oxidation -oxidation in the presence of UV light). Section 3 provides information on the various mechanisms of removal, the efficacy of each process, actual performance data for indirect potable recycling plants and analytical techniques for

monitoring process performance and predicting system failure. The technology should be fit for purpose and not over engineered leading to excessive costs.

Section 4 Monitoring

Monitoring is a key aspect to ensure the quality and safety of recycled water, and to confirm that quality guidelines are being met. Advances in analytical chemistry have made it possible to measure trace chemicals in wastewater at low concentrations. Chemical analysis and *in vitro* testing used to determine exposure, while *in vivo* bioassays are used to measure effect. Chemical analytical methods as well as bioanalytical toxicity testing and online monitoring methods are discussed in Section 4. Sampling and extraction methods are also discussed as this is a critical component in the monitoring process.

An issue sometime raised with water recycling schemes is one relating to mixtures of low concentration of chemicals that individually are with acceptable guidelines. A framework for consideration of mixtures and the so called 'unknown unknowns' using the suite of monitoring methods is represented as a decision tree in Figure 4-1.

Section 5 Public health surveillance and exposure from sources other than water

The Australian Drinking Water Guidelines (ADWG) including drinking water treatment chemicals (Chapter 8 of ADWG) is to ensure that at the point of consumption, water supplies meet rigorous guidelines which have been promulgated to ensure public safety. Water suppliers have generally adopted the HACCP principle in the management of the engineering process of water treatment. In these circumstances public health surveillance is unlikely to be necessary, other than where breakthrough has taken place or where there is evidence of community illness that might be associated with waterborne exposure to chemicals of interest.

There are three possible ways in which surveillance could be pursued:

- surveillance of the presence of a hazard – hazard surveillance
- the establishment of exposure - exposure surveillance
- where effects have become established associated with these exposures - outcome surveillance.

We consider that the first of these has the greatest power to prevent illness by removing any possibility of exposure. There is however a stage before hazard surveillance which involves appropriate controls on the presence of hazards using HACCP, or similar risk management, principles.

If surveillance is considered necessary it can be used to identify and trace waterborne health hazards and outcomes associated with them. However, if the water recycling facility is operating within its design parameters and meets Australian Drinking Water Guidelines, guidelines developed as part of this paper and all other regulatory expectations, it would be unlikely that surveillance beyond that already established as part of the normal process of recycled water management would be necessary.

Drinking water is one of a number of different sources for ingestion of chemical contaminants. Exposure can also occur due to other environmental factors such as food consumption, airborne contamination and use of pharmaceuticals and personal care products. Food exposure is the most likely exposure for a range of ingested chemical contaminants. There is substantial literature on the presence of toxic metals, pesticides and even radiological chemicals as anthropogenically derived food contaminants quite apart from the presence of natural toxins such as those produced

by fungi and plants. Section 5 of this report presents two case studies on exposure from others sources (1) bisphenol A (an industrial chemical), and (2) xenoestrogens (chemicals that can mimic the action of natural estrogen hormones).

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Glossary of abbreviations

ADI	acceptable daily intake
ADWG	Australian Drinking Water Guidelines
AICS	Australian Inventory of Chemical Substances
APE	secondary effluent
ATSDR	Agency for Toxic Substances and Disease Registry (US Department of Health and Human Services).
AVI	inherent availability
AVO	operating availability
AWT	advanced water treatment
BPA	bisphenol A
bw	body weight
CFR	Code of Federal Regulations (United States)
CHMP	Committee for Medicinal Products for Human Use (The European Medicines Agency)
CICAD	Concise International Chemical Assessment Documents (International Programme on Chemical Safety)
CRCWQT	Cooperative Research Centre for Water Quality and Treatment
CERHR	Center for the Evaluation of Risks to Human Reproduction
CR_X	Cancer Risk for exposure X
CTE	AWT effluent
DDD	dichloro-diphenyl-dichloroethane
DDE	dichloro-diphenyldichloro-ethylene
DDT	dichloro-diphenyl-trichloroethane
DNA	deoxyribonucleic acid
DWG	drinking water guideline
E1	estrone
E2	estradiol
E3	estriol
EC	European Commission
EC JRC	European Commission Joint Research Centre
ECVAM	European Centre for the Validation of Alternative Methods
EDI	estimated daily intake
EDTA	ethylenediamine tetraacetic acid
EE/O	units, the electrical energy input per unit volume per log order of reduction
EE2	ethinylestradiol
EFSA	European Commission Scientific Committee on Food
EMEA	European Medicines Agency
enHealth	Environmental Health Council (Australia)
EnTox	National Research Centre for Environmental Toxicology
EU	European Union

FE	tertiary effluent
GAC	granular activated carbon
GC	gas chromatography
GU	Griffith University
GWR	groundwater replenishment
HACCP	Hazard Analysis and Critical Control Points
HCH	hexachlorocyclohexane
HCN	Health Council of the Netherlands
HPLC	high performance liquid chromatography
ICP-MS	inductively coupled plasma - mass spectrometry
ILSI	International Life Sciences Institute
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System (US EPA)
JECFA	Joint Expert Committee on Food Additives (FAO/WHO)
JMPR	Joint Expert Committee on Pesticide Residues (FAO/WHO)
K_{ow}	logarithm of octanol-water partitioning coefficient
LOD	limit of detection
LOQ	limit of quantitation
LTD	lowest daily oral therapeutic dose for an adult
LWA	Land and Water Australia
MCL	maximum contaminant levels
MS	mass spectral detectors
MWCO	molecular weight cut-off.
MWd	molecular width
NDEA	N-nitrosodiethylamine
NDMA	N-nitrosodimethylamine
NEPC	National Environmental Protection Council
NHMRC	National Health and Medical Research Council
NICEATM	National Toxicology Program Interagency Centre for the Evaluation of Alternative Toxicological Methods (US National Toxicology Program)
NICNAS	National Industrial Chemical Notification and Assessment Scheme
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NPDWS	National Primary Drinking Water Standards (US EPA)
NRA	National Registration Authority for Agricultural and Veterinary Chemicals
NRMMC	Natural Resource Management Ministerial Council
NSAIDs	nonsteroidal anti-inflammatory drugs
NZ MoH	New Zealand Ministry of Health
OECD	Organization for Economic Cooperation and Development
OEHHA	Office of Environmental Health Hazard Assessment.
P	proportion of risk
PAC	powdered activated carbon
PAHs	polyaromatic hydrocarbons

PCB	polychlorinated biphenyls
PDTA	(propylenedinitrilo)tetraacetic acid
POCIS	polar chemical integrative samplers
R	risk
RAW	raw wastewater
RfD	reference dose
RIVM	Dutch National Institute of Public Health and the Environment
SCADA	Supervisory Control and Data Acquisition
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products (EC)
SF	safety factor
SIDS	screening information data set (WHO)
SPMDs	semi-permeable membrane devices
S-TDI	surrogate tolerable daily intake
STP	sewage treatment plant
TD_{50}	tolerable dose
TDI	tolerable daily intake
TEF	toxicity equivalent factor
TEQ	toxicity equivalent
TGA	Therapeutic Goods Administration (Australian)
TOC	total organic carbon
TTC	threshold of toxicological concern
UK COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (UK)
UNEP	United Nations Environment Programme
UNSW	The University of New South Wales
US EPA	US Environmental Protection Agency
US FDA	US Food and Drug Administration
UV	ultraviolet radiation
V	volume
VOCs	volatile organic chemicals (compounds)
WHO	World Health Organisation

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SECTION 1 Introduction

1.1 The Project

This purpose of this project was to;

Investigate scientifically justified human based chemical quality guidelines for a range of recycled water uses that lead to human exposure. The sources to be considered in the review are primarily based on recycled water from sewage treatment plants, although this approach is equally amenable to such sourves as water mining from sewers and managed aquifer recharge.

Recommend appropriate source control and treatment technologies to reliably reduce chemical contaminants in recycled water to levels that are acceptably safe for the uses of recycled water shown above.

To recommend options (if any exist) for appropriate human health surveillance to detect any impacts on human health from chemicals from the uses of recycled water shown above.

This information is intended to perform two functions:

- to provide input to the Joint Steering Committee for the National Guidelines for Water Recycling in their consideration of Phase 2 of the guidelines, which includes providing guidance on recycled water for drinking.
- to provide a consistent, authoritative technical review of chemical hazards in recycled water to State and Territory governments that may be considering regulation of water recycling schemes involving a range of uses;

This report considers the greatest potential exposure to recycled water (by augmenting drinking water supplies) as the worst case scenario. Exposure due to irrigation of crops and industrial exposures as listed above are expected to be substantially less than through drinking water. Therefore, the guidelines proposed for drinking are expected to be protective of human health for all other recycled water applications as well.

Tasks identified by the consultancy brief:

1. *What are the chemicals of concern* (including mixtures and breakdown products) known to occur in recycled water from Australian sewage treatment plants or advanced water treatment plants that may cause human health impacts at exposures likely to be encountered in the uses of recycled water listed in Section 1.1? As well as contaminants released into the sewer, the study must also address disinfection byproducts formed or added during treatment and disinfection of recycled water, cyanobacterial toxins that may be produced during storage or use of the recycled water and naturally occurring chemicals. An indicative listing of chemicals, contaminant classes and interactions with any naturally occurring chemicals or chemicals added to the drinking water from the recycling process, to be considered will be initially developed by the consultant and further refined in discussion with the Recycled Water Quality Guidelines Study Steering Committee.
2. *What are the acceptably safe levels of human exposure* to these chemicals during approved uses of recycled water as specified in Section 1.0? Safe levels for chemical hazards, including endotoxins, will be established through the conduct of a chemical health risk assessment using a methodology acceptable to the Recycled Water Quality Guidelines Study Steering Committee.
3. Where it is not possible to determine acceptably safe levels of these contaminants, either from the scientific literature or expert opinion, what are *appropriate margins of safety for*

those chemicals known to occur in recycled water that would protect human health during approved uses of recycled water as specified in Section 1.0?

4. *What are the best methods* (i.e. most reliable and cost effective) *to reduce or remove these contaminants from source waters* (e.g., what is the relative importance of source control relative to treatment technologies)?
5. *What is the efficacy of specific recycled water treatment technologies* in reducing each of the contaminants or contaminant classes specified in Task 1 above to safe levels, and what are the performance reliability profiles of these technologies?
6. *What are the most practical means for monitoring these contaminants* (or their potential for health impacts) in water?
7. In addition to current monitoring methods for chemicals, the consultant will include consideration of:
    - direct online (i.e. real time) monitoring, including use of biosensors;
    - use of whole effluent toxicity (WET) testing using aquatic invertebrates or fish or bioassays using cultured human tissue; and
    - use of indicator or sentinel chemicals or surrogate/composite compounds (e.g. total organic carbon or total organic halogens
8. The consultant will make recommendations on the feasibility and design of public health surveillance programs and epidemiological studies that would be capable of detecting any impacts on human health from those uses of recycled water specified in Section 1.0.
9. In considering the uses specified in 1.0, the consultant's first priority in terms of timing will be given to use of recycled water to supplement drinking water supplies, to reflect the urgent water supply situation in some parts of Australia. If the scale of the consultancy requires staging of reports, recycled water for drinking will be addressed first.
10. To assist with communication of the outcomes of the Recycled Water Quality Guidelines Study, the consultant must provide data on comparative risk to the public from chemical contaminants found in other commonplace involuntary chemical exposures, such as daily food intake, urban air pollution and use of personal care products. For example, this could include relative quantities, and associated lifetime exposures, of selected contaminants such as Bisphenol A or NDMA in food versus recycled water that has been treated to meet drinking water guidelines.

1.2 Project Team

The project manager is Mr Haemish Middleton, NEPC Service Corporation.

The project steering committee is comprised of Haemish Middleton, NEPC; Dr David Cunliffe, SA Department of Health; Dr Greg Jackson, Qld Health; and Mr Paul Smith, National Water Commission.

This work is being carried out by a consortium from:

The National Research Centre for Environmental Toxicology (EnTox) - Professor Michael R. Moore and Drs Heather F. Chapman and Frederic D.L. Leusch

The University of NSW (UNSW) - Drs Greg Leslie and Stuart Khan

Toxikos Pty Ltd. - Dr Roger Drew and Mr John Frangos

Griffith University (GU) - Dr Glen Shaw

1.3 Project Appreciation

Advances in analytical chemistry have made it possible to measure trace chemicals in water at low concentrations. Some of the same compounds have also been found in waters receiving discharge of treated wastewater (Kolpin et al 2002; Daughton and Ternes 1999) in the USA. A number of these have been also been demonstrated experimentally to be bioactive at trace concentrations. In addition, some physiological changes in wildlife have been detected downstream of sewage treatment plant discharges demonstrating a probable link between exposure to effluent and the condition found in fish (Jobling and Tyler 2003). In spite of this evidence, a link to health effects in humans has not been conclusively demonstrated (WHO/IPCS 2002). Even so, such observations have placed trace chemicals in municipal wastewater squarely in the public eye. This becomes particularly evident as we move to consider recycled water for a myriad of applications including the augmentation of drinking water supplies, fire fighting and irrigation of food crops, amongst other end use applications. Water quality becomes an important consideration in addition to quantity of water available for reuse.

Phase 2 of the Australian Guidelines for Water Recycling will include an additional three modules in addition to those including in the Phase 1 Guidelines. These include stormwater[1], modified aquifer recharge and augmentation of drinking water supplies (NEPC 2006 TOR this tender). This has motivated questions related to the fate and effects (if any) of new emerging chemical contaminants during wastewater treatment, advanced water treatment of recycled water and in drinking water.

It is now widely recognised that communication of risks associated with chemicals and the ever expanding range of applications of recycled water is an important component of project implementation. This report will not report specifically on communication as it is outside the terms of reference of this project, but it is important to understand that the perception of risk associated with recycled water derived from wastewater is likely to exceed the quantitative risks identified in the assessment process and subsequent setting of guidelines, particularly in the use of recycled water for augmenting drinking water supplies.

A number of relevant studies have been conducted in Australia in recent years. That information will not be reproduced except in summary, where required, in the context of this document. This document will expand and build on existing knowledge, focussing on Australian experiences, but will consider overseas data where this data is unavailable in Australia.

[1] There is an assumption that sewage water will present the worst case scenario therefore detailed consideration of stormwater will not form part of this document. Stormwater will be included only where relevant to the overall discussion.

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SECTION 2 Setting guidelines for chemicals in drinking water augmented with recycled water

2.1 Overview

Whatever the source of water — treated sewage, stormwater or traditional sources such as rivers, reservoirs or groundwater — it will contain a variety of chemicals. This chapter explains the process for setting guidelines to protect human health from chemicals in drinking water when recycled water is used as a source. The process described in this report was used to set the drinking water guidelines summarised in Table 2-11 at the end of this chapter; Box 2-1 explains what is meant by the term 'drinking water guideline' (DWG).

Essentially the DWG is the concentration of chemical in drinking water that will not cause harm should the water be drunk for extended periods of time, even over a lifetime. The drinking water guidelines recommended in this document have been developed for the protection the 'end-of-pipe' consumer, that is the person who drinks the water. The overriding philosophy applied in this document is that drinking water produced from source water that may contain recycled water should be at least as safe as that from traditional water sources. Consequently, the recommended guidelines have been established in a way that is consistent with approaches currently used in Australia and internationally for setting health protective guidelines for chemicals potentially found in food, water and/or air. The main focus of this chapter is the process for setting guidelines for chemicals for which no drinking water guideline is available.

The process for setting a DWG, and hence the DWGs herein, apply to drinking water sourced from any raw water supply (e.g. reservoirs, rivers, stormwater, groundwater, rain water, industrial wastewater, mine waters) as well as from secondary treated sewage water. For the purpose of identifying the chemicals of interest in this document, recycled water is defined as being the secondary treated effluent from a sewage treatment plant since this is currently envisaged to be the most realistic/likely source of large volumes of currently 'wasted' water that could be economically salvaged and treated in order to augment urban drinking water supplies.

Box 2-1: Meaning of the term 'Drinking Water Guideline'

Throughout this chapter, the term 'drinking water guideline' refers to a concentration of chemical in drinking water delivered to the consumer that may, either in whole or in part, include recycled water. The Australian Drinking Water Guidelines (NHMRC-NRMMC 2004) explains the rationale behind a guideline value for a particular chemical as follows:

the concentration that, based on present knowledge, does not result in any significant risk to the health of the consumer over a lifetime of consumption and is consistent with water of good quality. The health related guideline values are very conservative, and are calculated using a range of safety factors. They always err on the side of safety, particularly where scientific data are inconclusive or where the only data available are from animal studies.'

In other words, if the water complies with the drinking water guidelines, then drinking water augmented with recycled water is safe to drink. Short periods of consuming water containing chemicals at concentrations higher than the guideline values do not necessarily equate with a high likelihood of adverse health effects. The probability of an adverse health effect depends mainly on the actual concentration of chemical in the water and the length of time it was consumed.

The general approach to interpreting chemical monitoring data in drinking water relative to chemical standards and guidelines is that any excursion beyond an established standard or guideline value should trigger further investigation (PC 2000, NHMRC-NRMMC 2004).

If any water analysis showed that chemical concentrations were higher than the recommended DWGs, then contingency plans should be implemented. This may include hazard identification, risk assessments, increased monitoring and/or enhanced treatment to decrease the chemical concentration in the water to, or below, the value of the DWG before the drinking water could be delivered to the consumers. It stands to reason that if the recycled water complies with the chemical (and microbiological) guidelines, the water could readily be added to existing raw water sources (i.e. reservoirs or rivers) without compromising the eventual quality of the drinking water made from the source water. Whether the practice of adding recycled water with chemical concentrations higher than the DWGs and relying on dilution as a mitigation strategy in the receiving existing source water is a water management issue and not considered in this document. In every situation, the paramount consideration is that the drinking water at the 'end of the pipe' meets the chemical criteria in this document.

As a matter of principle, it is recognised that if recycled water is added to existing raw source water, the addition should not compromise the ecological status of the receiving waters[2]. Since chemical concentration criteria for the protection of the aquatic environment are usually lower than that required to ensure the safety of human health, meeting ecological requirements prior to discharging recycled water into potable raw water sources will not compromise human health. It is important to understand that because a chemical has been reported to potentially have an impact on an organism in the environment if the organism is exposed to high concentrations, it does not necessarily mean there is potential for human health effects. There are many factors that need to be considered before it can be assumed there is potential for impact on human health. Without undertaking those considerations it is incorrect to assume human health effects could occur on the basis of information obtained from ecological or non-mammalian studies.

[2] The information and guidance contained in Australian and New Zealand Guidelines for Fresh and Marine Water Quality (ANZECC 2000) will inform the reader regarding the essential requirements for protection of the aquatic environment.

An important feature of the methodology adopted for establishing drinking water guidelines in this report is that it draws on best practice, nationally and internationally, currently in place for establishing health protective guidelines for chemicals that could be in food, water and/or air. All these approaches used to set guidelines are founded on the elementary medical and toxicological principle that the 'dose makes the poison'. Throughout the world, in all jurisdictions, human health guidelines for chemicals in food, water and/or air are based on the fundamental fact that for the vast majority, if not all chemicals there is a safe level of exposure that is without adverse health effects[3].

For many of the chemicals found in recycled water there may already be an existing guideline for the amount allowed in drinking water that is safe. Those guidelines have been carried forward in the recommendations of this report.

This report does not replace the current Australian guidelines for chemicals in drinking water, rather, because there are chemicals in recycled water for which a drinking water guideline does not exist, this report supplements the information contained in the current National Health and Medical Research Council guidelines (NHMRC-NRMMC 2004). Chemicals of interest[4] for which there is not a current drinking water guideline fall into two categories, those that have health and/or toxicological information that would enable a drinking water guideline to be established, but hasn't, and chemicals that do not have such data and therefore a guideline cannot be set using traditional approaches.

For the former group of chemicals, safe drinking water concentrations (the guidelines) are established in this report in the same manner as the NHMRC for deriving the existing drinking water guidelines (NHMRC-NRMMC 2004). It is known that the chemicals and materials currently used in the production and distribution of drinking water may release a number of substances into the water. Internationally, these chemicals (and materials) undergo rigorous health impact evaluation prior to them being permitted for making and supplying drinking water. The DWG setting methods used in this report for recycled water are consistent with the risk assessment techniques used to evaluate and approve the chemicals (and materials) currently employed in manufacturing drinking water[5].

For those chemicals for which health data are not available at this time, the recommended guidelines herein have been derived using the approaches of the US Food and Drug Authority (US FDA), and the World Health Organisation (WHO), for setting guidelines for minor chemical contaminants that could be introduced into food during manufacture (FDA 2006, WHO 1987). These approaches are based on the regulatory principle of the threshold of toxicological concern (TTC). For some classes of chemicals that may be present in recycled water (e.g. various chemicals from food or vegetable matter, chemicals in personal care products, and certain

[3] There are some chemicals, relatively few and notably those that cause cancer by altering the DNA (ie the genotoxic carcinogens) for which there is, in theory at least, no absolute safe level of exposure. It is assumed there is some level of theoretical risk associated with any amount of exposure. Nevertheless there is a practical 'safe exposure' level that is negligible or *de minimus* risk. Depending on country and/or jurisdiction this equates to calculated risks of cancer of one in a million to one in ten thousand. See the Section 'Step 5' for consideration of 'threshold' vs 'non-threshold' chemicals in standard setting.

[4] Chemicals of interest are defined in Section 'Step 1' below. They are primarily those chemicals that have been found in the effluent of secondary sewage treatment either in Australia or overseas, included are chemicals of general interest to the community.

[5] For more information on the international evaluation schemes for water treatment chemicals see the report *"Overview of National and International Guidelines and Recommendations on the Assessment and Approval of Chemicals used in the Treatment of Drinking Water".* This report was prepared in 2003 for the National Health and Medical Research Council's Drinking Water Treatment Chemicals Working Party and is available at www.nhmrc.gov.au/publications/synopses/_files/watergde.pdf

household chemicals) human safety assessments have already been undertaken, either of the chemical *per se* or the formulated product, prior to being made available to the general public. It would therefore not be expected that the presence of these chemicals at low concentrations in drinking water would constitute a health hazard. Conversely, it is possible that there may be chemicals present in recycled water for which a prior safety evaluation has not been undertaken. The processes described herein enable DWGs for such chemicals in recycled water to be established. In essence the TTC extends the concept of acceptable daily intake[6] (ADI) that underpins most existing health based guidelines.

Chemical mixtures

There are no standardised procedures for incorporating potential effects of mixtures — additive, synergistic or suppressive — into the process of setting guideline values for regulatory purposes. Because of inherent uncertainties in the range and concentrations of possible components of complex mixtures in an environmental situation, it is generally not possible to use such information in setting standards.

There are established methods for aggregating estimates of risk when the composition of a chemical mixture is known or can be inferred using relevant data. Such methods usually aggregate risk by assuming that risks are additive, but this assumption implies that chemicals producing the same adverse health outcome act in the same way, which may not be the case. For example, endocrine disruption can operate through different receptors, pathways and signalling webs, and it is difficult to establish whether mixtures of endocrine disrupting chemicals will produce additive effects (with or without synergistic or antagonistic interactions), particularly at the low levels typically associated with environmental exposure. Therefore, when dealing with mixtures of chemicals in water or other media, quantitative health risk assessment tends to focus solely on the major individual contributors to risk.

Where chemicals in mixtures are at concentrations far below their individual toxicological thresholds (ie below individual guideline values), any additive or antagonistic effects are unlikely to contribute significantly or measurably to overall risk. Thus, the international regulatory approach to dealing with mixtures is to ensure that guideline values for individual chemicals are well below the concentrations required to produce an adverse health effect. This means that, even if mixtures contain multiple substances that cause the same effect by the same biological mechanism, the combined concentrations will still be well below toxicological thresholds. The process outlined in this document for determining guideline values for individual chemicals is sufficiently conservative (through the application of safety factors) to be consistent with the international regulatory approach. The process used means that compliance with individual guideline values will protect public health in schemes where recycled water is used to augment drinking water supplies.

[6] The nomenclature of acceptable daily intake (ADI) has generally been superseded by the term tolerable daily intake (TDI) in the vocabulary of many regulatory agencies. The same concept is called the reference dose (RfD) by the US EPA. All these terms are essentially interchangeable.

2.2 Process for setting guidelines

Figure 2-1 schematically outlines the standard setting process undertaken in this document. This section discusses each of the steps outlined in the diagram. The application of the process is illustrated with a wide range of chemicals that have been detected in wastewater that need to be removed through treatment before this recycled water is used to augment drinking water supplies. The chemical data presented here was sourced up to June 2007. The processes described in this report for establishing drinking water guidelines can be applied to any chemical compound identified from any water source, now and into the future.

2.2.1 Step 1 - Chemicals of Interest

The first step in the decision tree for setting drinking water guidelines is to list the chemicals of interest. These could include chemicals that have been found in the effluent of secondary sewage treatment either in Australia or overseas (it is assumed that sewage used as source of recycled water to augment drinking water supplies will be subject to secondary treatment at a minimum) and are therefore chemicals of general interest to the community, regulators, scientists and plant operators.

All domestic and industrial wastewater, and other potential 'non-traditional' drinking source waters will not directly enter the drinking water treatment facilities, instead, they must undergo secondary treatment (at a minimum) prior to further treatment at an advanced water treatment plant, and then eventually enter the drinking water treatment facility.

Therefore recycled water to be used as source water for drinking water treatment is going to be secondary (minimally) treated effluent from municipal sewage treatment plants. These will vary on quantity (size of plants) and quality (secondary treatment efficiencies). These sewage treatment facilities may also be processing influent water from a variety of sources including domestic and trade wastewater from industry, as well as some stormwater runoff. The primary list of chemicals of interest (Table 2-1) is therefore comprised of chemicals that have actually been found in secondary effluents from Australian municipal sewage treatment plants. Therefore, chemicals found in raw sewage, in primary treated sewage, or in other potential sources of recycled water (e.g. stormwater) are not considered here.

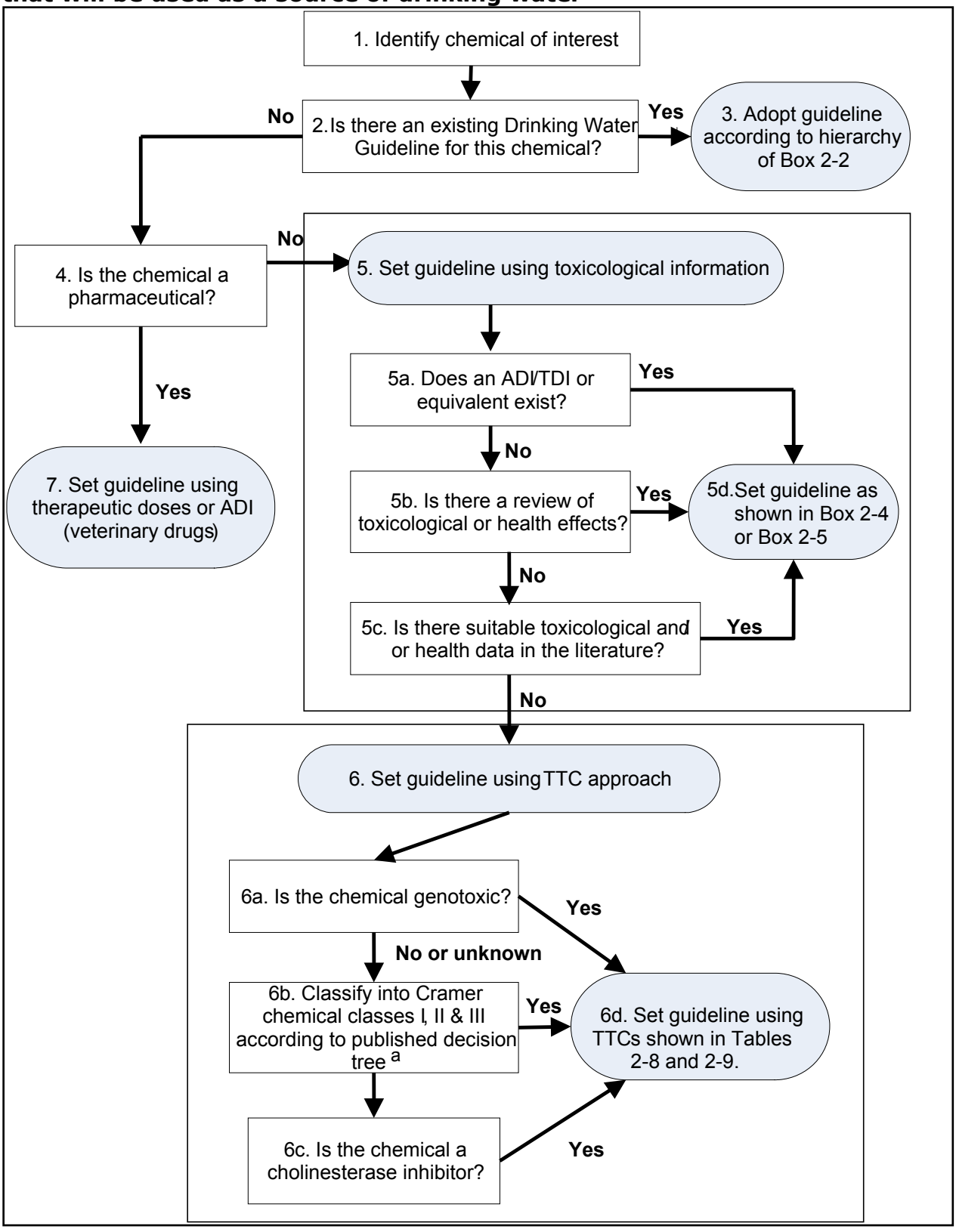
It is recognised that the extent of 'seek and measure' activities for chemicals in secondary effluent from Australian sewage treatment facilities may be limited relative to overseas efforts. Consequently, in order to ensure as many chemicals of interest that may realistically be present in Australian recycled water were considered for guideline setting, chemicals found in overseas sewage effluents equivalent to Australian effluents were compiled into a separate list of chemicals of interest (Table 2-2).

Included in Table 2-2 are chemicals identified in surface waters (streams and rivers) that have been a source of raw water for drinking water.

Also, to identify other chemicals of concern to the general public, advice was taken from community comments and consultations. Finally, recommendations for the inclusion of chemicals were sought from various Australian water authorities and government agencies. All chemicals nominated by the interested parties are captured in either Table 2-1 or Table 2-2.

The data in Tables 2-1 and 2-2 are not exhaustive but are representative of the range of chemical types and classes that could be present in secondary treated sewage effluent. The data are used in this report to develop and illustrate the approach taken for setting guideline values. This approach can be applied to any chemical of interest.

Figure 2-1: Decision tree for setting guidelines for chemicals in recycled water that will be used as a source of drinking water



ADI = Acceptable Daily Intake; TDI = Tolerable Daily Intake; TTC = Threshold of Toxicological Concern.
[a] Guideline values for chemicals that cannot be classified are calculated using the generic TTC.

Table 2-1: Compounds identified in secondary-treated sewage effluent in Australia

(Values in bold font have been recommended as DWG as described in Step 2 of Figure 2-1)

Chemical Name	DWG (µg/L)	Concentration found in effluent (µg/L)	Reference
PESTICIDES			
Acetylcholinesterase inhibitors			
Azinphos-methyl	**3** [a] 20 [c]	<LOD (0.5) - 2.1	A
Bromophos-ethyl	**10** [a] 0.5 [d]	<LOD (0.5) - 0.13	A
Carbendazim	**100** [a]	0.17 - 0.3	A
Chlorpyrifos	**10** [a] 30 [b] 90 [c] 0.5 [d]	<LOD (0.5) - 0.7	A
Chlorpyrifos-methyl	**0.5** [d]	<LOD (0.5) - 1.7	A
Demeton-S	- *	<LOD (0.5) - 3	A
Diazinon	**3** [a] 20 [c] 0.5 [d]	<LOD (0.5) - 3.2	A
Dichlorvos	**1** [a] 0.5 [d]	<LOD (0.5) - 1.1	A
Dimethoate	50 [a] **6** [b, i] 20 [c] 0.5 [d]	<LOD (0.5) - 1.9	A
Ethion	**3** [a] 0.5 [d]	<LOD (0.5) - 1.8	A
Ethoprophos	**1** [a] 0.5 [d]	<LOD (0.5) – 2	A
Fenthion (fenthion-methyl)	**0.5** [d]	<LOD (0.5) - 2.4	A
Malathion	**900** [b] 190 [c] 0.5 [d]	0.57	A
Ethyl parathion	**10** [a] 50 [c] 0.5 [d]	<LOD (2) - 2.2	A
Methyl parathion	**100** [a] 0.5 [d]	<LOD (2.0) - 2.8	A
Organochlorine pesticides			
4,4'-DDT	**20** [a, h] 1 [b] 0.5 [d]	<LOQ (0.01)	A
Chlordane	**1** [a] 2 [f]	<LOQ (0.5)	A
Endosulfan sulfate	**30** [a] 0.5 [d]	<LOD (0.01) - 0.25	A
Pentachlorophenol	**10** [a] 9 [b] 1 [f] 60 [c]	<LOD (0.05) - 0.18	A
Other pesticides			

Chemical Name	DWG (µg/L)	Concentration found in effluent (µg/L)	Reference
2,4,6-Trichlorophenol	**20** [a] 200 [b] 5 [c]	<LOD (0.015) - 0.054	A
2,4-D (2,4-Dichlorophenoxyacetic acid)	**30** [a] 30 [b] 70 [f] 100 [c]	<LOD (0.05) - 4.6	A
2,4-Dichlorophenol [k]	**200** [a] 200 [b] 900 [c]	<LOD (0.015) - 0.316	A
2-Chlorophenol [k]	**300** [a] 200 [b]	<LOD - 5.5	A
Atrazine	**40** [a, j] 2 [b] 3 [f] 5 (incl. metabolites) [c] 0.5 [d]	0.21 - 0.88	A
Dichloroacetic Acid [k]	**100** [a] 50 [b]	<LOD (0.01) - 0.50	A
Diuron	**30** [a] 150 [c]	0.26 - 0.29	A
Metolachlor	**300** [a] 10 [b] 50 [c]	<LOD (0.1) - 0.37	A
N,N-diethyltoluamide (DEET)	- *	<LOD (0.01) - 0.78	A
Simazine	**20** [a, j] 2 [b] 4 [f] 10 [c] 0.5 [d]	0.9 - 1.04	A
Thiophanate	**5** [a] 0.5 [d]	<LOD (8.0) – 12	A
Trichloroacetic acid	**100** [a] 200 [b]	<LOD (0.01) - 3.52	A
Trifluralin	**50** [a] 20 [b] 45 [c] 0.5 [d]	<LOD (0.02) - 0.15	A
PHARMACEUTICALS			
Antibiotics			
Amoxycillin	- *	<LOD - 0.02	C
Erythromycin	- *	<LOD (0.05) - 0.92	A
Azithromycin	- *	<LOD (0.05) - 0.072	A
Cefaclor	- *	<LOD - 1.21	C
Cephalexin	- *	<LOD - 0.09	C
Chloramphenicol	- *	<LOD - 0.023	A
Chlortetracycline	- *	<LOD - 0.163	A
Ciprofloxacin	- *	0.13	C
Clarithromycin	- *	0.24	B
Clindamycin	- *	<LOD (0.05) - 0.120	A
Doxycycline	- *	0.003 - 0.03	C
Enrofloxacin	- *	<LOD - 0.002	A
Erythromycin	- *	0.009	C
Lincomycin	- *	<LOD - 0.015	C

Chemical Name	DWG (µg/L)	Concentration found in effluent (µg/L)	Reference
Monensin	- *	0.003 - 0.08	A
Nalidixic acid	- *	<LOD - 0.22	C
Norfloxacin	- *	<LOD - 0.09	C
Penicillin G	- *	<LOD - 0.03	C
Penicillin V	- *	<LOD - 0.21	C
Roxithromycin	- *	<LOD - 0.68	B
Sulfamethoxazole (SMXZ)	- *	<LOD - 0.52	A
Sulfathiazole	- *	<LOD - 0.002	C
Tetracycline	- *	<LOD - 0.02	C
Trimethoprim	- *	<LOD (0.05) - 0.35	A
Tylosin	- *	0.02	C
Estrogenic compounds			
17α-ethynylestradiol	- *	<LOD - 0.002	D
17β-estradiol	- *	0.0006 - 0.027	A
Estrone	- *	<LOD (0.0001) - 0.039	D
Non-Steroidal Anti-Inflammatory Drugs			
Aspirin	- *	<LOD (0.1) - 2.1	A
Diclofenac	- *	<LOD (0.1) - 0.81	B
Ibuprofen	- *	<LOD (0.1) - 0.3	A
Indomethacin	- *	<LOD (0.1) - 0.19	A
Ketoprofen	- *	<LOD (0.1) - 0.11	A
Naproxen	- *	<LOD (0.1) - 0.57	A
Other pharmaceuticals			
Pentetic acid	**250** (analogy with EDTA)	<LOD (1.0) - 8.5	A
Clofibric acid	- *	0.1	A
Alprazolam	- *	<LOD (0.20) - 0.62	A
Carbamazepine	- *	15.9 – 27.3	A
Gemfibrozil	- *	<LOD (0.1) - 0.42	A
Iohexol	- *	<LOD (0.1) - 1.6	A
Iopamidol	- *	<LOD (0.1) - 1.6	A
Iopromide	- *	<LOD (0.1) - 1.8	A
Methotrexate	- *	1	B
Sulfasalazine	- *	<LOD - 0.12	C
Temazepam	- *	0.65 - 1.64	A
Diazepam	- *	0.9 - 2.92	A
OTHER COMPOUNDS			
Polychlorinated Biphenyls & Dioxins			
2,3,3',4,4',5-Hexachlorobiphenyl (PCB156)	Refer to Table 2-3	4.6 - 8.2 pg/L	A
2,3,3',4,4'-pentachlorobiphenyl (PCB105)		16.4 - 27.4 pg/L	A
2,3',4,4',5-Pentachlorobiphenyl (PCB118)		44.2 - 63.6 pg/L	A
2,4,5,3',4',5'-Hexachlorobiphenyl (PCB167)		<LOD (2) - 3.8 pg/L	A
3,4,5,3',4',5'-Hexachlorobiphenyl (PCB169)		<LOD (2) - 2 pg/L	A
Octachlorodibenzo-p-dioxin (OCDD)		53.6 - 100.2 pg/L	A
PCB77	0.5 [e]	<LOD (5) - 5.8 pg/L	A
Inorganic compounds			

Chemical Name	DWG (µg/L)	Concentration found in effluent (µg/L)	Reference
Boron	**4,000** [a] 500 [b] 5,000 [c] 1,000 [d]	100	A
Bromine	- *	490 – 570	A
Chlorine	**5,000** [a] 5,000 [b] 4,000 (Maximum Residual Disinfectant Level) [f]	<LOD (50) - 70	A
Fluoride	**1,500** [a] 1,500 [b] 4,000 [f] 1,500 [c] 1,500 [d]	700 - 1,200	A
Iodine	- *	41 - 48	A
Nitrate (NO_3^-)	**50,000** [a] 50,000 [b] 10,000 [f] 45,000 [c] 50,000 [d]	4,000 - 10,000	A
Nitrite (NO_2^-)	**3,000** [a] 200 [b] 1,000 [f] 500 [d]	500 - 4,300	A
(Propylenedinitrilo) tetraacetic acid (PDTA)	- *	<LOD (1.0) - 27	A
1,1-Dichloroethene	**30** [a] 30 [b] 7 [f] 14 [c]	30	A
2,6-dichlorophenol	- *	<LOD (0.015) - 0.026	A
4-Chlorophenol	- *	<LOD (0.010) - 0.016	B
4-Nonylphenol	- *	<LOD (0.1) - 2.9	A
4-tert-octylphenol	- *	<LOD (0.0005) - 0.014	A
Bisphenol A	- *	0.0005 - 0.032	A
Bromoacetic Acid [k]	- *	<LOD (0.01) - 0.35	A
Bromochloroacetonitrile [k]	- *	<LOD (0.01) - 0.25	A
Bromochloromethane [k]	- *	66	A
Bromodichloromethane [k]	250 (total THM) [a] **6** [b] 100 (total THM) [c] 100 (total THM) [d]	0.05 - 0.08	A
Bromoform [k]	250 (total THM) [a] **100** [b] 100 (total THM) [c] 100 (total THM) [d]	<LOD (5) - 81	A
Chloroform (Trichloromethane)[k]	250 (total THM) [a] **200** [b] 100 (total THM) [c] 100 (total THM) [d]	0.13 - 0.37	A
Coumarin	**0.5** [d]	<LOD (0.01) - 1.3	A
Diatrizoic acid	- *	<LOD (0.1) - 1.9	A

Chemical Name	DWG (µg/L)	Concentration found in effluent (µg/L)	Reference
Dibromochloromethane [k]	250 (total THM) [a] **100** [b] 100 (total THM) [c] 100 (total THM) [d]	0.04 - 0.12	A
Dibutyltin	- *	<LOD (0.025) - 0.034	A
Dichloroacetonitrile [k]	**2** [b] 10 [e]	<LOD (0.01) - 0.72	A
Dichloromethane (Methylene chloride)	**4** [a] 20 [b] 5 [f] 50 [c]	<LOD (2) - 10.8	A
Di-n-butyl phthalate	- *	<LOD (0.005) - 0.89	A
Ethylenediaminetetraacetic acid (EDTA)	**250** [a] 600 [b]	0.7 - 21	A
Monobutyltin	- *	<LOD (0.025) - 0.09	A
Nitrilotriacetic acid	**200** [a] 200 [b] 400 [c]	<LOD (0.5) - 12	A
N-Nitrosodiethylamine	**0.01** [e]	<LOD (0.002) - 0.003	A
N-Nitrosodimethylamine	**0.01** [e]	0.004 - 0.021	A
N-nitrosomorpholine	- *	<LOD (0.001) - 0.012	A
Nonylphenol	- *	0.014 - 0.185	A
Tributyl phosphate	**0.5** [d]	<LOD (0.01) - 0.19	A
METALS			
Antimony	**3** [a] 6 [f] 6 [c] 5 [d]	<LOD (0.1) - 0.38	A
Arsenic	**7** [a] 10 [b] 10 [f] 25 [c] 10 [d]	1.3 - 1.5	A
Barium	**700** [a] 700 [b] 2,000 [f] 1,000 [c]	3	A
Cadmium	**2** [a] 3 [b] 5 [f] 5 [c] 5 [d]	0.1	A
Cesium	- *	<LOD (0.1) - 0.29	A
Chromium	**50** [a] 50 [b] 100 [f] 50 [c] 50 [d]	<LOD (0.1) - 2.06	A
Cobalt	- *	0.6	A
Copper	**2,000** [a] 2,000 [b] 1,300 [f] 2,000 [d]	<LOD (5) - 120	A

Chemical Name	DWG (µg/L)	Concentration found in effluent (µg/L)	Reference
Lead	**10** [a] 10 [b] 15 [f] 10 [c] 10 [d]	10	A
Lithium	- *	22	A
Magnesium	- *	15,660 - 23,500	A
Manganese	**500** [a] 400 [b]	76	A
Molybdenum	**50** [a] 70 [b]	3	A
Nickel	**20** [a] 20 [b] 20 [d]	5	A
Rubidium	- *	0.52 - 33.8	A
Scandium	- *	0.2 - 0.3	A
Selenium	**10** [a] 10 [b] 50 [f] 10 [c] 10 [d]	0.8 - 1	A
Silicon	- *	1,100 - 1,300	A
Strontium	- *	<LOD (0.1) - 129	A
Titanium	- *	<LOD (0.1) - 21.8	A
Tungsten	- *	<LOD (0.1) - 6.17	A
Vanadium	**50** [g]	<LOD (0.1) - 1.88	A
RADIONUCLEOTIDES			
Alpha particles	0.5 Bq/L [a] 15 pCi/L [f]	<LOD (0.4) - 0.19 Bq/L	A
Beta particles and photon emitters	0.5 Bq/L [a] 4 millirems per year [f]	0.7 - 1.2 Bq/L	A

LOD = Limit of Dectection

* No drinking water guideline available prior to this document (see Table 2-11 for suggested guideline value set in this study).

a Australian Drinking Water Guideline (NHMRC–NRMMC 2004).

b WHO Drinking Water Guideline (WHO 2006), if necessary corrected to apply carcinogenicity risk of 10^{-6}.

c Canadian Drinking Water Quality Guidelines (Health Canada 2006).

d European Council Directive 98/83/EC (EU 1998)

e US EPA Health Limit

f US EPA National Primary Drinking Water Standards – Maximum Contaminant Level (US EPA 2006).

g US EPA

h Both the Australian and WHO DWG's for DDT are based on TDI's from WHO/JMPR. The WHO DWG is based on an allocation of 1% to water to account for increased used. The Australian guideline use a 10% allocation on the basis that "Such a low percentage of the ADI was considered inappropriate for Australia, where usage of DDT has declined markedly". The Australian DWG was there used in this document.

i The WHO evaluation of dimethoate is more recent and is documented, whereas documentation was not available for the Australian DWG.

j The difference between the Australian and WHO DWG for pentachlorophenol relates to the proportionality factor – the Australian DWG uses a higher proportionality factor because the NHMRC-NRMMC (2004) reported the pesticide does not appear in the Australian diet.

k Disinfection byproduct.

References for Table 2-1:

A. Unpublished confidential data for chemicals found in secondary treated effluent from around Australia on at least one occassion.
B. Review of Health issues Associated with Potable Reuse of wastewater (RTF200/00). Department of Health and Aged Care. Commonwealth of Australia, 2001.
C. Costanzo and Watkinson (2007)
D. LWA (2007)

Table 2-2: Compounds identified in secondary-treated sewage effluent in other countries

(Values in bold font have been recommended as DWG as described in Step 2 of Figure 2-1).

Chemical Name	DWG (µg/L)	Concentration (µg/L)	Reference	Country
PESTICIDES				
Acetylcholinesterase inhibitors				
Tri(dichlorisopropyl) phosphate [1]	- *	<LOD (0.1) - 0.16	A	US
Triphenyl Phosphate [1]	- *	<LOD (0.1) - 0.22	A	US
Tris(2-chloroethyl)phosphate[1]	- *	<LOD (0.04) - 0.54	A	US
Organochlorine pesticides				
4,4'-DDE	**20** [a] 1 (DDT & metabolites) [b] 0.5 [d]	<LOD (0.001) - 0.145	C	CY
Lindane (γ-BHC; γ-HCH; gamma-HCH; gamma-BHC)	**20** [a] 2 [b] 0.2 [e] 0.5 [d]	<LOD (0.05) - 0.11	A	US
α-BHC (alpha-BHC; alpha-lindane)	**20** [a] 0.5 [d]	<LOD (0.001) - 0.084	C	CY
β-BHC (beta-BHC; beta-lindane)	**20** [a] 0.5 [d]	<LOD (0.002) - 0.33	C	CY
Other pesticides				
4-Nitrophenol	- *	2.3	D	ES
Alachlor	**2** [b] 2 [e]	<LOD (0.1) - 0.167	E	US
Cypermethrin	Unlikely to occur in drinking water [b] 0.5 [d]	<LOD - 0.08	F	ES
Tributyltin	**1** (tributyltin oxide) [a]	0.021	G	CH
PHARMACEUTICALS				
Androgenic compounds				
Androsterone	- *	<LOD (0.05) - 0.214	A	US
Testosterone	- *	<LOD (0.005) - 0.214	A	US
Antibiotics				
Demeclocycline	- *	0.09 - 1.12	H	US
Oxytetracycline (Terramycin)	- *	0.66	H	US
Sulfadimethoxine (SDMX)	- *	<LOD (0.05) - 0.06	A	US
Sulfamethazine	- *	<LOD – 0.68	H	US
Sulfamethizole	- *	<LOD (0.05) - 0.13	A	US
β-andrenergic blockers				
Betaxolol	- *	0.19	B	DE
Bisoprolol	- *	0.37	B	DE
Carazolol	- *	0.12	B	DE
Metoprolol	- *	2.2	B	DE
Nadolol	- *	0.06	B	DE
Propranolol	- *	0.29	B	DE

Chemical Name	DWG (µg/L)	Concentration (µg/L)	Reference	Country
Timolol	- *	0.07	B	DE
Estrogenic compounds				
17α-estradiol	- *	<LOD (0.005) - 0.074	A	US
Equilenin	- *	<LOD (0.005) - 0.278	A	US
Equilin	- *	<LOD (0.005) - 0.147	A	US
Estriol	- *	<LOD (0.005) - 0.051	A	US
Mestranol	- *	<LOD (0.005) - 0.407	A	US
Norethindrone	- *	<LOD (0.005) - 0.872	A	US
Progesterone	- *	<LOD (0.005) - 0.199	A	US
Stigmastanol	- *	<LOD (2) - 4	A	US
Non-Steroidal Anti-Inflammatory Drugs				
Dipyrone	- *	2.4 - 7.5	F	ES
Fenoprofen	- *	0.062 - 0.759	H	CA
Tolfenamic acid	- *	1.6	B	DE
Other pharmaceuticals				
Acetaminophen	- *	<LOD (0.032) - 4.3	F	ES
Antipyrine	- *	0.41	B	DE
Atorvastatin	- *	0.019 - 0.044	H	CA
Benzafibrate	- *	4.6	B	DE
Cimetidine	- *	<LOD (0.007) - 0.58	A	US
Clenbuterol	- *	0.05	B	DE
Codeine	- *	<LOD (0.01) - 1.0	A	US
Cotinine	- *	<LOD (0.023) - 0.9	A	US
Cyclophosphamide	- *	0.02	B	DE
Dehydronifedipine	- *	<LOD (0.01) - 0.03	A	US
Diltiazem	- *	<LOD (0.012) - 0.049	A	US
Enalaprilat	- *	<LOD (0.15) - 0.046	A	US
Fluoxetine	- *	0.05 – 0.142	H	CA
Isophosphamide	- *	1.91 (Hospital effluent)	B	DE
Metformin (1,1-Dimethylbiguanide)	- *	<LOD (0.003) - 0.15	A	US
Salbutamol	- *	0.035	B	DE
Salicylic acid	- *	3.6 - 59.6	H	US
Terbutaline	- *	0.12	B	DE
Other compounds				
Polychlorinated Biphenyls & Dioxins				
2,7-Dichlorodibenzo-p-dioxin (DCDD)	Refer to Table 2-3	<LOD - 1.2	F	ES
Inorganic Compounds				
Bromide	- *	<LOD (20) - 280	E	US
Musks				
2,4,6-Trinitro-1,3-dimethyl-5-tert-butylbenzene	- *	0.025 - 0.036	B	DE
Galaxolide	- *	0.036 - 0.152	B	DE
Musk ketone	- *	0.14 - 0.41	B	DE
Musk tibetene	- *	0.00004	B	DE
Pentamethyl-4,6-dinitroindane (Musk moskene)	- *	0.0083	B	DE
Polyaromatic Hydrocarbons (PAHs)				
Anthracene	- *	<LOD (0.05) - 0.11	A	US

Chemical Name	DWG (µg/L)	Concentration (µg/L)	Reference	Country
Benzo(a)pyrene	**0.01** [a] 0.7 [b] 0.2 [e] 0.01 [c] 0.01 [d]	<LOD (0.05) - 0.24	A	US
Fluoranthene	**4** [f]	<LOD (0.03) - 1.2	A	US
Naphthalene	- *	<LOD (0.02) - 0.08	A	US
Phenanthrene	- *	<LOD (0.06) - 0.53	A	US
Pyrene	- *	<LOD (0.03) - 0.84	A	US
Other compounds				
1,7-Dimethylxanthine (Paraxanthine)	- *	0.11 - 3.1	A	US
2,5-Dihydroxybenzoic acid	- *	0.59	B	DE
2,6-di-tert-butyl-1,4-benzoquinone (2,6-bis(1,1-dimethylethyl)-2,5-Cyclohexadiene-1,4-dione)	- *	<LOD (0.1) - 0.46	A	US
2,6-di-tert-butylphenol (2,6-bis(1,1-dimethylethyl)phenol)	- *	<LOD (0.08) - 0.11	A	US
2-Phenylphenol	**1,000** [f]	<LOD - 2.6	B	DE
4-Acetyl-6-t-butyl-1,1-dimethylindan	- *	0.002 - 0.008	B	DE
4-cumylphenol	- *	0.14 - 0.98	F	ES
4-methylphenol (p-Cresol)	- *	<LOD (0.04) - 0.54	A	US
5-methyl-1H-benzotriazole	- *	<LOD (0.1) - 2.4	A	US
6-Acetyl-1,1,2,4,4,7-hexamethyltetraline	- *	0.024 - 0.088	B	DE
Acetophenone	- *	<LOD (0.15) - 0.41	A	US
Anatoxin-A	A potent alkaloid toxin derived from cyanobacteria	8.5 (finished water)	I	US
Benzyl chloride	- *	0.0018	J	JP
Butylated hydroxy toluene (2,6-Di-tert-Butyl-p-Cresol)	- *	0.1	A	US
Butylated hydroxyanisole (3-tert-butyl-4-hydroxy anisole)	- *	<LOD (0.12) - 0.2	A	US
Caffeine	- *	<LOD (0.014) - 6.0	A	US
Chlorophene	- *	<LOD - 0.71	B	DE
Cholesterol	- *	<LOD (1.5) - 10	A	US
Coprostanol (5beta-Cholestan-3beta-ol)	- *	<LOD (0.005) - 9.8	A	US
Diatrizoate Sodium	- *	0.23	B	DE
Phenol	- *	<LOD (0.25) - 1.3	A	US
Phthalic anhydride	- *	0.25 - 1	A	US
Tri(butyl cellosolve) phosphate (ethanol,2-butoxy-phosphate)	- *	<LOD (0.2) - 6.7	A	US
Triclosan	- *	0.08 - 0.40	F	ES
METALS				
Silver	**100** [a]	<LOD (0.1) - 0.1	E	US

[1] Although this compound is not a pesticide it is an acetyl cholinesterase inhibitor. It has been grouped in this way for comparison and association with other acetyl cholinesterase inhibitors, usually pesticides.

* No drinking water guideline available prior to this document (see Table 2-11 for suggested guideline value set in this study).

a Australian Drinking Water Guideline (NHMRC–NRMMC 2004).
b WHO Drinking Water Guideline (WHO 2006), corrected as necessay to apply carcinogenicity risk of 10^{-6}.
C Canadian Drinking Water Quality Guidelines (Health Canada 2006).
d European Council Directive 98/83/EC (EU 1998)
e US EPA National Primary Drinking Water Standards – Maximum Contaminant Level (US EPA 2006).
f WHO health-based value. Health based values are usually very conservative and err on the side of caution. The concentrations likely to be found in drinking water are, for some compounds, much lower than the health-based value derived for that compound. Therefore, under usual conditions, due to the low toxicity of the compound, the compound is unlikely to represent a hazard to human health. For this reason sometimes only a health-based value is given and a guideline value not derived. (WHO 2006)

Country codes:
CH - Switzerland
CY - Cyprus
DE - Germany
ES - Spain
JP - Japan
US - United States of America

References for Table 2-2:
A Kolpin et al (2002)
B Daughton & Ternes (1999)
C Fatta et al. (2007)
D Castillo et al. (1997)
E Denver Water, unpublished data
F Gomez et al. (2007)
G Fent (1996)
H Costanzo & Watkinson (2007)
I Richardson (2003)
J OECD (2002)

2.2.2 Step 2 – Existing drinking water guidelines

Having identified chemicals of interest, the next step is to determine whether a drinking water guideline has already been set for that chemical. Box 2-2 lists established drinking water guidelines produced by authorities around the world, as examples of the type of document that can be searched to match against the chemicals of interest. The sources are listed in order of preference of acceptance, based on recommendations from the National Health and Medical Research Council (NHMRC) and the enHealth Council of Australia in relation to risk assessment of environmental hazards (enHealth 2004).

In developing the guideline values given in this document (summarized in Table 2-11), the guidelines listed in Box 2-2 were searched. In line with the recommendations of the NHMRC and enHealth Council, drinking water guidelines from Australia and the World Health Organization (WHO) were given preference over those of other authorities.

The guidelines for chemicals given in the Australian Drinking Water Guidelines (ADWG) (NHMRC–NRMMC 2004) are largely based on the methods and outcomes of the relevant WHO publications. However, there are some distinctions between the WHO and Australian Drinking Water Guidelines (ADWG); for example:

- the WHO guidelines assume a bodyweight of 60 kg, to cater for the lighter bodyweights of developing countries; however, Australian guidelines assume a bodyweight of 70 kg
- for carcinogenic compounds, the WHO guidelines use a risk assessment calculation, with the guideline value set at the concentration that would give rise to a risk of one additional cancer per 100 000 people, whereas the Australian guideline values for these types of compounds are based on a risk of one in a million. Where WHO guidelines for non-threshold chemicals have been used in this appendix, the values have been adjusted to take into account the lower level of risk used in the Australian guidelines.

When setting drinking water guidelines, the WHO uses the best scientific and human health advice available. For example, preparation of the 2004 WHO Guidelines for Drinking Water Quality involved the participation of 490 leading scientists from nearly 90 developing and developed countries (WHO 2006). If properly implemented, the WHO guidelines ensure the safety of drinking water supplies by reducing to safe levels the concentration of contaminants that are known to be potentially hazardous to health. Therefore, it is advisable to use drinking water guidelines from WHO or the ADWG where available. The guideline setting processes of the NHMRC and WHO have both regulatory and social acceptance in Australia. Drinking water guidelines from the other authorities listed in Box 2-2 should be used only where there is appropriate documentation to allow the basis of the guideline to be summarized.

Unlike the Australian Drinking Water Guidelines, aesthetic considerations of taste are not explicitly considered in the guidelines established in this report. This report only addresses health considerations in the guideline setting process. It is however possible to review the health based guidelines for organoleptic compliance should the need arise.

Box 2-2: Example sources of drinking water guidelines (DWGs)[a].

NHMRC-NRMMC (2004). Australian Drinking Water Guidelines (ADWG). National Health and Medical Research Council (NHMRC) in collaboration with the Natural Resource Management Ministerial Council (NRMMC). http://www.nhmrc.gov.au/publications/_files/adwg_11_06.pdf

WHO (2006). Guidelines for Drinking-Water Quality, third edition, incorporating first addendum http://www.who.int/water_sanitation_health/dwq/gdwq3rev/en/index.html

EU (1998). Council Directive 98/83/EC of 3 November 1998 on the quality of water intended for human consumption, Official Journal L 330, 05/12/1998 p 0032-0054. http://ec.europa.eu/environment/water/water-drink/index_en.html

NZ MoH (2005). Drinking Water Standards for New Zealand, New Zealand Ministry of Health, Wellington, New Zealand, http://www.moh.govt.nz/moh.nsf/0/12F2D7FFADC900A4CC256FAF0007E8A0/$File/drinkingwaterstandardsnz-2005.pdf .

Health Canada (2006). Guidelines for Canadian Drinking Water Quality. http://www.hc-sc.gc.ca/ewh-semt/pubs/water-eau/doc_sup-appui/index_e.html

US EPA (2007). Drinking Water Contaminants Lists. http://www.epa.gov/safewater/hfacts.html Office of Water United States Environmental Protection Agency.

OEHHA (Various dates). Public Health Goal for Chemical Substances in Drinking Water Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. http://www.oehha.ca.gov/water/phg/allphgs.html

US EPA (Various dates). Health Advisories for Drinking Water Contaminants. Office of Water, United States Environmental Protection Agency.

[a] Whilst this is an hierarchical list of sources, if an agency has established a DWG which is more up-to-date using recent appropriate data and/or assessment techniques then that DWG should be considered *in lieu* of a 'hierarchical' DWG.

2.2.3 Step 3 – Adopt drinking water guideline

In this document, existing drinking water guidelines, where available, have been adopted. As explained above for Step 2, values published in the ADWG (NHMRC–NRMMC 2004) or the WHO guidelines (WHO 2006) were given priority in adopting guidelines for Table 2-11.

Where no drinking water guideline has been published for a chemical, it is necessary to set a guideline, using the process outlined in Figure 2-1.

2.2.4 Step 4 - Is the chemical a pharmaceutical?

The method used to set a drinking water guideline will depend on the nature of the chemical involved. Where the chemical is not a pharmaceutical, a guideline is set using one of the following:

Step 5 — toxicological information, such as Acceptable Daily Intake (ADI), Tolerable Daily Intake (TDI), a review of toxicological or health effects, or suitable data from the literature.

Step 6 — an appropriate Threshold of Toxicological Concern (TTC).

In the case of pharmaceuticals, a guideline is set using lowest daily therapeutic doses or ADIs (for veterinary pharmaceuticals) where available plus safety factors (Step 7).

2.2.5 Step 5 - Set drinking water guideline using toxicological information

This section describes the method used to set guidelines for non-pharmaceutical chemicals for which toxicological information is available. Steps 5a–5c cover the process of determining whether the appropriate information exists, and Step 5d explains how to set the guideline using that information.

Steps 5a–5c
The method used in this document for setting drinking water guidelines from health or toxicological data is the same as used by the NHMRC for establishing the ADWG (NHMRC–NRMMC 2004). It is also the same as that used by the WHO for its drinking water guidelines (WHO 2006).

There is a general rule in toxicology that adverse effects elicited by chemicals over a short (ie acute) exposure period require higher exposures than for the same effects to be caused with long term (ie chronic) exposures. For this reason, chronic health guidelines are set assuming lifetime exposure, and are much lower than guidelines set for acute exposures. Consequently, and in conjunction with the safety factors, short periods of consumption of water containing chemicals at concentrations higher than the guideline values does not equate with high likelihood or imminent adverse health effects. Actually, the probability of an adverse health effect being realised is a combination of both the actual concentration of chemical in the water and the length of time it was consumed.

Because people consume water all their life, the health effects of concern for chemical contaminants in water are those related to lifetime (ie chronic) exposure. Epidemiological surveillance methods or case control studies are not particularly useful, or appropriate, for determining dose-response health effects from chemical exposure via drinking water. The most common approach is to gather information on toxicological or health effects chemical by chemical. The whole database is then evaluated to find one or more pivotal studies identifying the critical adverse effects and the exposure (dose) to be used in the calculation of a drinking water guideline.

It was not viable (or indeed necessary) for such detailed data evaluations to be undertaken in developing this document. Therefore, in setting guidelines for non-pharmaceuticals for these guidelines, appraisals undertaken by other competent organisations (listed in Box 2-3) were used to obtain the following:

Step 5a — ADIs or TDIs established by Australian, WHO and other agencies (note: reference doses (RfD) are the equivalent safe ingestions of chemicals established by United States health agencies).

Step 5b — If an ADI, TDI , or equivalent, for a chemical of interest has not been established by a credible authority, then appropriate information is sourced from a toxicological profile written by one of the authorities in Box 2-3.

Step 5c — If suitable toxicological information is not obtained from Steps 5a or 5b, then a search of the scientific literature is undertaken.

In gathering toxicological information for use in calculating drinking water guidelines for this document, the information was appraised according to the principles for hazard evaluation described by the NHMRC (2006), the enHealth Council (enHealth 2004), and the WHO (WHO 1987, 1990, 1994, 1999).

The drinking water guidelines calculated from toxicological information and the methodology described below are summarised in Table 2-11.

Step 5d

Step 5d is to use the data obtained at Steps 5a–5c to set guidelines. The particular mathematical method employed to calculate the DWG from the data depends on whether the chemicals are regarded as possessing a 'threshold' for their toxicological effects. It is convenient to separate chemicals into 'threshold' or 'non-threshold chemicals', this is explained as follows:

'Threshold' chemicals — these are chemicals where effects are only observed above a certain threshold dose; no effects are observed at doses below this threshold. Experimentally the threshold dose is determined as that which causes no adverse effect in laboratory animals, often the threshold dose concept is expanded to include the dose that causes no demonstrable effect (adverse or otherwise). These doses are respectively called the 'no observed adverse effect level' (NOAEL) and the 'no observed effect level' (NOEL). With appropriate consideration of the uncertainty in extrapolating effects in animals to humans, and the variability in human response, exposures below these levels are deemed to be safe.

'Non-threshold' chemicals — typically these are chemicals that may cause cancer by inducing genetic mutations (in deoxyribonucleic acid (DNA)). A mutation is potentially capable of playing a role in the cascade of events that could lead to cancer if it occurs at the correct location on the gene(s) at the right time, and is not fixed by cellular repair mechanisms. Hence on theoretical grounds, even if it may be extremely unlikely for a cancer to occur, it is generally considered there is no absolute safe level of exposure to genotoxic carcinogens. Calculation of drinking water guidelines for non-threshold chemicals are developed from extrapolation of dose response relationships determined from effects elicited in laboratory animals, or workers, by doses considerably higher than those that will be encountered in drinking water. Because carcinogenesis depends upon statistical biochemical/DNA events occurring in a defined progression, a guideline is set at a very low probability of the effect occurring; this is a chance of one in a million.

Box 2-3: Example sources of health and toxicological information

Listed below are examples of the type of document that can be used a sources of health and toxicological information for setting drinking water guidelines, as covered in Steps 6a and 6b of the process outlined in Figure 2-1.

TGA (2006). Acceptable daily intakes for agricultural and veterinary chemicals. Australian Therapeutic Goods Administration http://www.tga.gov.au/docs/html/adi.htm. Last updated 31st December 2006.

IPCS (various dates). Environmental Health Criteria Monograph Series from the International Programme on Chemical Safety (IPCS) - a cooperative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP). www.inchem.org

IPCS CICAD (various dates). Concise International Chemical Assessment Documents from the International Programme on Chemical Safety (IPCS) - www.inchem.org

WHO JECFA (Various dates). Safety Evaluation of Certain Food Additives and Contaminants. WHO Food Additives Series: Prepared by the Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) World Health Organization, Geneva www.inchem.org

WHO JMPR (Various dates). Safety Evaluation of Pesticide Residues. WHO Pesticide Residue Series: Prepared by the Meeting of the Joint FAO/WHO Expert Committee on Pesticide Residues (JMPR) World Health Organization, Geneva www.inchem.org

US EPA (various dates). Integrated Risk Information System. Full Summary – Various Chemical Substances. www.epa.gov/iris United States Environmental Protection Agency.

ATSDR (Various dates). Toxicological Profiles for Chemical Substances, Agency for Toxic substances and Disease Registry (ATSDR), US Department of Health and Human Services.

RIVM (2001). Re-evaluation of Human Toxicological Maximum Permissible Risk Levels, Dutch National Institute of Public Health and the Environment (RIVM 2001).

EU (various dates). European Union Existing Chemical Risk Assessment Reports, European Commission, Joint Research Centre European Chemical Bureau, European Union. http://ecb.jrc.it/esis/index.php?PGM=ora

Health Canada (2004). Health-based guidance values for substances on the second priority substances list. Minister of Supply and Services Canada. http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl2-lsp2/guidance_values.pdf

A. Threshold chemicals (Non-pharmaceuticals):

Wherever possible, human data is used for calculating the guideline, but since there is a paucity of such information extrapolations are usually made from toxicological information obtained from experimental studies in animals. Because there is uncertainty associated with the extrapolation from effects seen in animals to what might be expected in humans, a number of uncertainty factors [referred to as 'safety factors' in the ADWG (NHMRC–NRMMC 2004)], are applied to ensure humans are protected from adverse health effects. Furthermore, because it is possible that exposure of an individual to a particular chemical may occur through environmental exposures other than water, only a portion of the overall safe chemical dose is allocated to water when setting a guideline. Text Box 2-4 and Box 2-5 summarise the mathematical mechanics of setting a drinking water guideline using toxicological information.

Box 2-4: Calculation of DWGs using toxicological data: *Threshold Chemicals*

The equation used by the NHMRC-NRMMC (2004) for establishing a health protective drinking water guideline is:

$$\text{Drinking water guideline} = \frac{\text{animal dose} \times \text{human weight} \times \text{proportion of intake from water}}{\text{safety factor} \times \text{volume of water consumed}}$$

$$\text{Guideline (mg/L)} = \frac{\text{NOAEL (mg/kg bw/d)} \times \text{bw (kg)} \times P}{SF \times V \text{ (L/d)}} \quad \text{.....Equation 1}$$

Where:

Animal dose (NOAEL) = No observed adverse effect level (NOAEL) from a chronic animal study expressed as mg compound/kg body weight/day. When the animal dose is different from this appropriate safety factors are used.

Human weight (bw) = the assumed average body weight of an Australian adult (70 kg), or a 2 year old child (13 kg).

Volume of water (V) = 2 L/d for an adult or 1 L/d for a 2 year old child; considered by NHMRC-NRMMC (2004) as appropriate for Australian conditions (see text for more information).

Safety factor (SF) = up to 10,000. Allocated according to advice in Australian Drinking Water Guidelines and NHMRC (1999) (see text).

Proportion from water (P) = Variable but default is 10% or 20% (i.e. P =0.1 or 0.2). (See text).

The general form of Equation 1 is used by most countries to set drinking water guideline values; the assumptions used in the equation are conservative and err on the side of safety. Box 2-5, below, provides further information on V, SF and P.

- The acceptable daily intake (ADI), or tolerable daily intake (TDI) is an estimate of the daily amount of substance that can be ingested over a life time that is considered safe. It is calculated by dividing the NOAEL by safety factors. Thus in Equation 1 the term NOAEL/SF can be replaced by the ADI or TDI. That is:

$$\text{Guideline (mg/L)} = \frac{\text{TDI (mg/kg bw/d)} \times \text{bw (kg)} \times P}{V \text{ (L/d)}} \quad \text{.....Equation 2}$$

- Equation 2 is that used by WHO (2006) and invoked at **Step 5a** in Figure 1.

Box 2-5: Notes on values given in Box 2-4

Volume of water consumed
The assumed amount of water consumed is the same as that used by the ADWG (NHMRC–NRMMC 2004) to be appropriate for Australian conditions. However, in some circumstances (eg in the tropical North of Australia), water intake may be more than the assumed 2 L/day. Although amounts of 5 L/day may sometimes be ingested, this intake is unlikely to be sustained over a long period of time.

As discussed in Section A2.2, the ADWG assume a human body weight of 70 kg, the same as that used by other developed countries, whereas the WHO assumes 60 kg.

Proportion of safe intake allocated to water
The assumed amount of chemical ingested per day that is regarded as safe (ie the TDI or its equivalent) may come from sources other than drinking water. To ensure the TDI is not exceeded, the amount that can come from drinking water must therefore be a fraction of the total allowed. Ideally, background intakes (ie intakes other than from drinking water) should be determined for each chemical of interest. However, it is not feasible to do this for all the chemicals considered in this document. According to the ADWG.

- for chemicals used commercially or industrially, a default apportionment of 10% of total intake is allocated to water.
- for chemicals that are not used commercially or industrially, a higher proportion of intake (usually 20% but sometimes 80% or even 100%) is assumed to come from drinking water.

In deriving drinking water guidelines, Health Canada has a default assumption that 20% of the TDI may be associated with the water (Health Canada 2006). In this report, the default assumptions of the ADWG have been adopted unless particular circumstances mean that they are inappropriate. Hence, it has been assumed that, for industrial chemicals, 10% of the TDI is from water, and for all other substances, 20% of the TDI is from water. For individual chemicals, these apportionments may be adjusted as information on background intakes from sources other than drinking water becomes available.

The Australian Inventory of Chemical Substances (AICS) was used to judge whether a chemical is in commercial use in Australia. The ACIS lists chemicals approved for industrial use in Australia under the National Industrial Chemical Notification and Assessment Scheme (NICNAS). It does not include active chemicals of pharmaceutical, or agricultural or veterinary preparations, but does include cosmetic ingredients.

Safety Factors
Safety factors can be thought of as translating the dose causing no adverse effects in experimental animals (ie the NOAEL) into an equivalent no effect dose for humans, taking into account the uncertainties involved with such extrapolation. In many other countries, and in other applications in Australia, safety factors are referred to as uncertainty factors. The advice given by the NHMRC (1999) on the size and technical application of uncertainty factors was used in this document in **Step 5d** of the process shown in **Figure 2-1**.

B. Non-threshold chemicals.

Chemicals which may cause cancer, by directly altering either the structure or function of DNA (i.e. genetic mutations), are not considered to exhibit absolute safety, i.e. there is no unconditional threshold below which effects do not occur. Instead, it is deemed there is some risk associated with any level of exposure. The Australian Drinking Water Guidelines for these types of chemicals are based on a consideration of:

- the limit of determination (LOD) based using the most common analytical method;
- the concentration, calculated by the WHO using a risk assessment model, that could give rise to a risk of one additional cancer per million people, if water containing the chemical at that concentration were consumed over a lifetime; and
- a value based on a threshold effect calculation, with an additional safety factor for potential carcinogenicity.

In this document, for a chemical whose carcinogenicity has been characterised by experimental determination of potency, i.e. by derivation of a 'slope factor', the calculation of a drinking water guideline is undertaken with a target risk of one in a million (1×10^{-6}). The resulting drinking water guideline is taken to mean that if a population of one million people were to consume water at the concentration of the drinking water guideline for a lifetime then one additional cancer might plausibly be expected to occur in that population as a result. In reality, since cancer potency factors are usually calculated as an upper estimate (i.e. at the upper 95% confidence limit), the drinking water guidelines are set for much lower risks than 10^{-6}.

Box 2-6: Calculation of DWG using toxicological data: *Non-threshold Chemicals*

The equation used to set drinking water guidelines for non-threshold chemicals is:

$$\text{Drinking water guideline (mg/L)} = \frac{R \times P \times bw\ (kg)}{SlF\ (mg/kg/day)^{-}1 \times V\ (L/day)}$$

Equation 3

Where:

R = risk, one in a million (1×10^{-6}).
P = proportion of risk from water; variable but default is 10% or 20% (ie P = 0.1 or 0.2).
bw = bodyweight (70 kg for an adult).
SlF= slope factor $(mg/kg/day)^{-1}$; cancer potency factor from literature.
V = volume of water consumed (2L/day).

The tables below show the recommended drinking water guidelines for chemicals established for this report based on:

- toxicological information; that is, using an agency-derived TDI or cancer risk (Table 2-3)
- an agency derived NOEL (Table 2-4)
- an agency derived cancer slope factor for non-threshold chemicals (Table 2-5).

Table 2-3: Recommended drinking water guidelines established from toxicological information (ie with an agency-derived TDI, ADI or RfD)

Chemical name	Tolerable intake (mg/kg bw/day)	Reference	Recommended drinking water guideline (µg/L) [a]
Pesticides			
4-Nitrophenol	0.008 [d]	US EPA (2006) [o]	30 [b]
Cypermethrin	0.05 [f]	TGA (2006)	175 [b]
Demeton-S	0.00004 [d, i]	US EPA (1988b)	0.15 [b]
Other compounds			
Inorganic			
Bromide/bromine	1 [f]	TGA (2006) JMPR (1988)	7,000 [c]
Iodine	0.017 [e]	JECFA (1988b)	60 [b]
Organic			
2,6-dichlorophenol [q]	0.003 [e] (total dichlorophenols)	RIVM (2001)	10 [b]
4-Chlorophenol [q]	0.003 [e] (total monochlorophenols)	RIVM (2001)	10 [b]
4-methylphenol (p-Cresol)	0.17 [f] (total cresols) [h]	WHO (1995)	600 [b]
Acetophenone	0.1 [d]	US EPA (1989)	400 [b]
Bisphenol A	0.05 [d, e]	US EPA (1993a) EFSA (2006)	200 [b]
Bromochloromethane	0.01 [d]	US EPA (2006) [o]	40 [b]
Butylated hydroxyanisole	0.5 [f]	JECFA (1988a)	1750 [b]
Butylated hydroxytoluene	0.3 [f]	JECFA (1995)	1,000 [b]
Dibutyltin (DBT)	0.00025 [e, j]	EFSA (2004a)	2 [c]
Di-n-butyl phthalate	0.01 [e, k]	EFSA (2005)	35 [b]
Phenol	0.04 [e, m]	RIVM (2001)	150 [b]
Phthalic anhydride	2 [d]	US EPA (1988a)	7000 [b]
Polyaromatic hydrocarbons (PAHs)			
Anthracene	0.04 [e, g]	RIVM (2001)	150 [b]
Naphthalene	0.02 [d, l]	US EPA (1998)	70 [b]
Phenanthrene	0.04 [e]	RIVM (2001)	150 [b]
Pyrene	0.03 [d, n]	US EPA (1993b)	150 [b]
Dioxin-like compounds			
2,3,3',4,4',5-Hexachlorobiphenyl (PCB156)	Tolerable monthly intake for dioxin like substances is 70 pg TEQ/kg/month; this is equivalent to 2.3 pg TEQ/kg bw/day	NHMRC (2002)	16 pq TEQ/L [c, p] This recommended drinking water guideline is for the total of all dioxin-like substances in drinking water and needs to consider toxicity equivalent factors (TEFs) for individual compounds. The recommended guideline value for PCBs (dioxin like and non-dioxin like compounds) is 0.14 µg/L[L]
2,3,3',4,4'-pentachlorobiphenyl (PCB105)			
2,3',4,4',5-Pentachlorobiphenyl (PCB118)			
2,4,5,3',4',5'-Hexachlorobiphenyl (PCB167)			
2,7-Dichlorodibenzo-p-dioxin (DCDD)			
3,4,5,3',4',5'-Hexachlorobiphenyl (PCB169)			
Octachlorodibenzo-p-dioxin (OCDD)			

ADI = acceptable daily intake; RfD = reference dose; TDI = tolerable daily intake; TEQ = toxic equivalent

a Drinking water guideline calculated using Equation 2 in Box 2-4.
b Chemical may be in commercial use; proportion from water (P) = 10%.
c Chemical unlikely to be in commercial use; P = 20%.
d Reported as RfD.
e Reported as TDI.
f Reported as ADI.
g An RfD value of 0.3 mg/kg/day was reported for anthracene by US EPA (1993c).
h A TDI of 0.05 mg/kg bw/day has been reported for total cresols by RIVM (2001); however, the TDI was derived in 1991 and the documentation for its derivation is not available; therefore, the TDI from the more recent evaluation by WHO/IPCS (1995) was used. An intermediate duration oral minimal risk level (MRL) of 0.1 mg/kg/day (ATSDR 2006a) was also reported.
i The tolerable intake reported is for Demeton; that is, a mixture of Demeton-O and -S. An ADI value for Demeton-S was not found; hence, the guideline calculation is based on the RfD for Demeton.
j A group TDI of 0.00025 mg/kg bw/day is established for tributyltin, dibutyltin, triphenyltin and di-n-octyltin.
k Tolerable intake values for di-n-butyl phthalate were also reported as a TDI of 0.066 mg/kg bw/day (WHO 1997), an RfD of 0.1 mg/kg bw/day (US EPA 1990) and a TDI of 0.052 mg/kg bw/day (RIVM 2001). Recent scientific studies have focused on the developmental and reproductive effects of di-n-butyl phthalate. Because the EFSA (2004b) evaluation considered the recent studies on developmental and reproductive toxicity of di-n-butyl phthalate in context of modern risk assessment methods for assessing endocrine disruptors, the EFSA (2004b) TDI was used instead of the 1997 WHO value.
l A TDI of 0.04 mg/kg bw/day was reported for naphthalene by RIVM (2001).
m Tolerable intake values for phenol were also reported as a TDI of 0.06–0.2 mg/kg bw/day (WHO 1994b), a RfD of 0.3 mg/kg/day (US EPA 2002), an acute oral minimal risk level (MRL) of 0.6 mg/kg/day (ATSDR 2006b) and a TDI of 0.12 mg/kg bw/day (Health Canada 2004). The WHO (1994b) review was prepared by RIVM; thus, the RIVM (2001) value was considered an update of the risk assessment conducted in 1994 on behalf of the WHO.
n A 1×10^4 lifetime excess oral cancer risk was reported for pyrene as 0.5 mg/kg bw/day (RIVM 2001).
o No primary documentation could be located at the time of writing to support the reported value.
p The DWG for dioxin like compounds is for the sum of all dioxins, furans and PCBs calculated as TEQs using the toxicity equivalent factors (TEFs) reported in Van den Berg et al. (2006). The following dioxin like substances have been reported in Australian sewage effluent: octachlorodibenzo-p-dioxin (OCDD); 2,3,3',4,4',5-hexachlorobiphenyl (PCB156); 2,3,3',4,4'-pentachlorobiphenyl (PCB105); 2,3',4,4',5-pentachlorobiphenyl (PCB118); 2,4,5,3',4',5'-hexachlorobiphenyl (PCB167); 3,4,5,3',4',5'-hexachlorobiphenyl (PCB169); PCB77.
q Disinfectant byproduct.
L Total PCBs should be below a guideline value of 0.14 µg/L derived from an ADI of 0.02 ug/kg/day (US EPA 2006) and an allocation to water of 20%.

Table 2-4: Recommended drinking water guidelines for non-pharmaceuticals established from an agency-derived no observed effect level (NOEL)

Chemical name	Reported NOEL (mg/kg bw/day)	Reference	SF	Derived tolerable intake (mg/kg bw/day)	Recommended guideline value (µg/L) [a]
Pesticides					
N,N-diethyltoluamide (DEET)	75	COT/COM/COC (2002)	100	0.75	2,500 [b]
Other compounds					
Musks					
2,4,6-Trinitro-1,3-dimethyl-5-tert-butylbenzene (musk xylene)	10	SCCNFP (2004)	100	0.1	350 [b]
Galaxolide	50	HERA (2004)	100	0.5	1,750 [b]
Musk ketone	10	SCCNFP (2004)	100	0.1	350 [b]
Other organic compounds					
4-Nonylphenol (4NP)	15	EC(2002b)	100	0.15	500 [b]
4-tert-octylphenol	15	OECD(1995)	1000	0.015	50 [b]
Nonylphenol	15	EC(2002b)	100	0.15	500 [b]
Tri(butyl cellosolve) phosphate (ethanol,2-butoxy-phosphate)	15	WHO(2000)	1000	0.015	50 [b]

NOEL = no observed effect level; UF = uncertainty factor

a Drinking water guideline calculated using Equation 1 in Box 2-4, values have been rounded.

b Potentially in commercial use; hence P = 10%

Table 2-5: Recommended drinking water guidelines for non-threshold chemicals

Non-threshold chemicals	Cancer Slope Factor (mg/kg/day)	Reference	Recommended drinking water guideline (µg/L)
Benzyl chloride	-	US EPA (1994)	0.2 [a]
N-Nitrosomorpholine	6.7 $(mg/kg/day)^{-1}$	CAL EPA (1999)	0.001 [b,c]

a Reported drinking water concentration at a risk of 1 in 1 000 000.

b Drinking water guideline calculated using Equation 3.

c Chemical unlikely to be in commercial use; P = 20%.

2.2.6 Step 6 - Thresholds of toxicological concern

Guideline values for chemicals for which there are no established guidelines, and for which relevant health or toxicological information does not exist at this time (identified at Step 5c in Figure 2-1), are derived from Thresholds of Toxicological Concern (TTCs) or the NOEL that underpin the TTC as described in Steps 6a–6c. The TTC approach is not applied to pharmaceutical compounds (see Step 7), metals or dioxins.

In brief, if the chemical is genotoxic it is assumed the substance may be carcinogenic and a generic (default) TTC based on the carcinogenic chemical database of the US FDA and US EPA is used to set the drinking water guideline. If the chemical has not been demonstrated to cause genetic damage, then TTCs based on a quantitative structure activity classification scheme validated against a number of non-carcinogenic toxicological endpoints are used to establish the drinking water guideline. Detailed explanations of the underlying philosophy of the different TTCs are provided in Steps 6a – 6c. In Appendix 1, the TTCs used in setting drinking water guidelines have been tested against existing guidelines and no observed effect levels (NOEL) identified for chemicals with guidelines to make certain use of the TTCs will not compromise public health.

Step 6a — Is the chemical genotoxic?

The first step in the hierarchal application of the TTC concept is to determine if the chemical is genotoxic; that is, whether they have the ability to cause direct damage to DNA. Genotoxicity is a well-recognised toxicological mode of action through which chemicals may induce a cancer; thus, the supposition associated with genotoxicity is that the chemical may be a carcinogen of high potency. This is a very precautionary assumption. Genotoxicity does not automatically equate with the substance causing cancer in experimental animals, nor does it imply that substances carcinogenic to experimental animals are necessarily carcinogenic to humans. In addition, not all types of genotoxicity are associated with non-threshold carcinogenic responses[7] (CHMP 2006). However, since many more chemicals have been tested either *in vitro* or *in vivo* for broad genotoxic activity than have been tested for carcinogenicity, a protective approach is taken in setting drinking water guidelines for chemicals that do not have an existing guideline, and for which no health or toxicological data have been located.

For this report genotoxicity was assessed for listed chemicals for which no TDI or NOEL was identified. The results are shown in Table 2-6.

For genotoxic chemicals, i.e. those that pass through Step 6a of Figure 2-1, the 'generic' threshold of toxicological concern (TTC) (see below for additional information) is applied in place of the TDI in Equation 2 of Text Box 2-1 when setting the guideline for that chemical.

[7] Examples of mechanisms of genotoxicity that may lead to dose–response relationships with a threshold include interaction with the spindle apparatus of cell division leading to aneuploidy, topoisomerase inhibition, inhibition of DNA synthesis, overloading of defence mechanisms, metabolic overload and physiological perturbations (eg induction of erythropoeisis, hyper- or hypothermia) (CHMP 2006).

Table 2-6: Genotoxicity evaluation of substances without a TDI or NOEL.

Chemical Name	Genotoxic	Reference
Acetylcholinesterase inhibitors		
Triphenyl Phosphate [a]	?	WHO/SIDS (2002a)
Fire retardants		
Fyrol FR 2 (tri(dichlorisopropyl) phosphate) [a]	?	WHO (1998)
Tris(2-chloroethyl)phosphate [a]	?	WHO (1998)
Organic compounds		
2,4,6-Trinitro-1,3-dimethyl-5-tert-butylbenzene (musk xylene)	N	SCCNFP (2004)
Galaxolide	N [b]	SCCNFP (2004)
Musk ketone	N	SCCNFP (2004)
Musk tibetene	N [b]	SCCNFP (2004)
Pentamethyl-4,6-dinitroindane (Musk moskene)	N [b]	SCCNFP (2004)
(Propylenedinitrilo)tetraacetic acid (PDTA)	N	Structural features
1,7-Dimethylxanthine (Paraxanthine)	N [b]	WHO/SIDS (2002b)
2,5-Dihydroxybenzoic acid	N	JECFA (2002)
2,6-di-tert-butyl-1,4-benzoquinone (2,6-bis(1,1-dimethylethyl)-2,5-cyclohexadiene-1,4-dione)	Y [d] (DWG=0.014 µg/L) [h]	NICNAS (2001)
2,6-di-tert-butylphenol (2,6-bis(1,1-dimethylethyl)phenol)	N [b]	SCCNFP (2004)
4-Acetyl-6-t-butyl-1,1-dimethylindan	N [b]	
4-cumylphenol	N [e]	EC (2002b)
4-tert-octylphenol	N [e]	EC (2002b)
5-methyl-1H-benzotriazole	Y [f] (DWG=0.007 µg/L) [h]	HCN (2000)
6-Acetyl-1,1,2,4,4,7-hexamethyltetraline	N	Api & San (1999)
Bromoacetic Acid	N	WHO (2003a)
Bromochloroacetonitrile	N	WHO (2003b)
Caffeine	N	WHO/SIDS (2002b)
Chlorophene	N	WHO/SIDS (1998)
Cholesterol	N	IARC (1987)
Coprostanol (5beta-Cholestan-3beta-ol)	N [g]	IARC (1987)
Diatrizoate Sodium	?	
Diatrizoic acid	?	
Monobutyltin (MBT)	N	WHO (1990a)
Nonylphenol	N	EC (2002b)
Tri(butyl cellosolve) phosphate (ethanol,2-butoxy-phosphate)	N	WHO (1998)
Triclosan	N	NSCF (2004)

N = no; Y = yes; ? = unknown.

a There is insufficient information available to assess whether these compounds are genotoxic.

b Considered nongenotoxic on the basis of structural similarity to musk ketone and musk xylene.

c Information could not be located on the genotoxicity of paraxanthine, but the chemical is not expected to be genotoxic because it is a metabolite of caffeine, and caffeine has been assessed by WHO/SIDS (2002b) to be nongenotoxic.

d Considered genotoxic on the basis that quinones are chemically reactive and capable of forming adducts with DNA (NICNAS 2001).

e Alkylphenols were considered nongenotoxic based on structural analogy to nonylphenol.

f HCN (2000) considered the weight of evidence to indicate a potential for 1,2,3-benzotriazole to be a possible genotoxic carcinogen. Based on structural analogy, 5-methyl-1H-benzotriazole is considered genotoxic.

g Sterols as a chemical class are not regarded as genotoxic.

h The drinking water guideline is determined by use of the TTC of 0.02 µg/kg/d for genotoxic compounds as the TDI in Equation 2 and assignment of either 10% or 20% of the TTC to water, depending on whether the compound is likely to be in commercial use (see Step 6b for information on the genotoxic compound TTC and also Table 2-7).

Generic threshold of toxicological concern for genotoxic compounds

The US FDA (FDA 1995, CFR 2001) regulatory TTC is based on a carcinogenic potency database of over 500 chemicals examined in more than 3,500 experiments. The US FDA (FDA 1995, CFR 2001) and other leading researchers (Munro et al. 1996, 2002) have concluded that, if no toxicological data is available on a chemical upon which to derive a health based standard, intakes of 1.5 µg/person/d (0.02 µg/kg bw/d for a body weight of 70 kg[8]) are unlikely to result in appreciable health risk even if the substance was later found to be a carcinogen. According to Munro (1990), assuming 10% of chemicals are truly human carcinogens, a daily intake at the TTC of 0.02 µg/kg bw corresponds to a 96% probability that the lifetime risk of cancer would be less than the *de minimus* level of one in a million (1×10^{-6}).

The FDA regulatory TTC has been adopted by WHO and the European Community (EC 2003) as a threshold intake of minor substances in food that will trigger detailed risk assessments or experimental programs investigating the toxicity of the chemical. These authorities consider that there is very low health risk associated with this level of chemical intake. Below this level of intake, specific toxicity testing of the chemical is not warranted and only an abbreviated safety assessment, mainly focused on intake estimations, is undertaken (FDA 2006, EC 2003). The European Medicines Agency Committee for Medicinal Products for Human Use has proposed a TTC of 1.5 µg/day (i.e. 0.02 µg/kg bw/day) for genotoxic impurities in pharmaceuticals (CHMP 2004).

Because cancer caused by a genotoxic carcinogen usually occurs at chemical exposures much lower than those necessary to cause other effects, the numerical value of the TTC is higher for toxicological effects other than cancer. Consequently, in this publication, the FDA regulatory TTC is referred to as the 'generic' TTC[9]. The TTC estimate of 0.02 µg/kg bw/day is conservative, erring on the side of safety, because of the numerous compounding conservative assumptions used to derive the low-dose cancer risk estimates (Barlow et al 2001, Kroes et al 2004).

Kroes et al (2004) and Barlow (2005) report the conclusions of the Expert Group of the Threshold for Toxicological Concern Task Force of the European branch of the International Life Sciences Institute (ILSI). The group examined an extended carcinogenic data base (730 compounds) and specifically divided the compounds into the carcinogen structural alerts defined by Ashby and Tennant (1991). The expert group found there were some genotoxic carcinogens with potential potency that could represent a risk of greater than one in a million if ingestion occurred at the 'generic' TTC intake level over a lifetime. These substances were aflatoxin-like compounds, or were chemicals incorporating N-nitroso- or azoxy-functional groups. The expert group suggested that a TTC should not be derived for these compounds and that, if detected, they should be subject to individual risk assessments (Kroes et al 2004). This deliberation has been adopted in this document as a precautionary measure because it provides increased safety assurance. Aflatoxin-like compounds and azoxy-compounds have not been identified as issues in recycled water or drinking water. N-nitroso compounds such as NDMA and nitrosodiethylamine (NDEA) have been detected, but these have established guideline values. If compounds without established guideline values are identified, they should be subject to individual risk assessments

[8] It should be noted the TTC is usually expressed as an intake per person (i.e. mg/person/day) and that when correcting for body weight the European literature assumes a body weight of 60 kg. However in this document on setting standards for chemicals in potable water made from recycled water the default body weight of 70 kg for an adult male, as recommended by enHealth 2004 is used. Consequently the TTC's recommended in this report may be slightly lower from those reported in the scientific literature.

[9] The TTC of 0.02 µg/kg bw/day was determined by the US EPA from the experimental carcinogenic database as the 5th percentile intake associated with an upper bound lifetime cancer risk of one in a million (1×10^{-6}). The distribution of upper bound cancer potencies (ie intake at the 1×10^{-6} risk level) was constructed from linearised low-dose extrapolation calculated using the TD_{50} as the departure point for the extrapolation. The TD_{50} is the lifetime dose of carcinogen that causes cancer in 50% of the test animals. Kroes et al (2004) followed a similar methodology and noted the simple linear extrapolation from a 50% tumour incidence (the TD50) to a 1 in a million incidence was extremely conservative.

that should include consideration of toxicological data and the removal effectiveness of water treatment processes.

The ILSI assessment also noted there were approximately 2 - 3% of chemicals in their extended database, other than the ones named above, that presented a greater risk than one in a million at the TTC promulgated by the US FDA (1995). As a very conservative measure they recommended a TTC for such compounds (recognised as genotoxic carcinogens of high potency) of 0.15 µg/person/day (i.e. 0.002 µg/kg/d). This is ten times lower than the FDA adopted TTC. ILSI state "this threshold gives a 86–97% probability that any risk would be less than 1 in 106 if the intake were at or below the TTC, and the compound were to be a genotoxic carcinogen" (Kroes et al 2004).

In this guidance a very precautionary approach has been adopted. It has been assumed that any genotoxic compound could be a carcinogen of high potency. For these compounds the TTC recommended by ILSI (Kroes et al 2004, Barlow 2005) is used to derive a DWG. The lower TTC for carcinogens adopted by the US FDA (1995) is used for DWG derivation of those organic compounds compounds whose genotoxicity is unknown and which are not classifiable by ToxTree into a Crammer class. It should be noted this is a very conservative approach that provides a high degree of confidence in the safety of the DWG.

Step 6b — Use of 'structural' thresholds of toxicological concern

For chemicals that were not identified as being genotoxic in Step 6a, guideline values are derived from TTCs using structural information. The thresholds determined using this TTC concept are intakes of chemicals below which a given compound of known structure is not expected to present a toxicological concern. On the basis of classical pharmacological and toxicological concepts of dose response, exposure to trace levels of chemicals represents very low risks. TTCs have been developed for classes of substances with a systemic mode of toxicological action and with exposure by ingestion.

The TTC approach was for many years put forward as a pragmatic solution for addressing low concentrations of additives in food (Frawley 1967, Munro 1990, Munro et al 1996). It was first applied in a regulatory sense by the FDA (1995, CFR 2001) and was later used by the European Commission (EC) (2003) to address chemicals migrating from plastic packaging into food. Today, it is applied by the FDA, the EC and WHO (Joint FAO/WHO Expert Committee on Food Additives, JEFCA) in their deliberations on direct and indirect (ie contaminants) food additives, including flavouring substances (FDA 1995; JEFCA 1995; 1999; Munro et al 1999; EC 2003; Renwick 2004, 2005; EC JRC 2005). The TTC concept has also been adapted by Wilson et al (2000) for deriving criteria for soil risk management for chemicals of unknown toxicological hazard or potency at contaminated sites and as a risk assessment tool for low concentrations of chemicals in industrial emissions (Drew and Frangos 2006).

Recently, the TTC has been suggested as a means of judging whether ingredients at low concentration in personal and household-care products require toxicological testing (Blackburn et al 2005). Also, a scientific rationale based on the threshold of toxicological concern, has been proposed by Dolan et al (2005) for estimating ADIs for compounds with limited or no toxicity data, to support pharmaceutical manufacturing operations. However, Delany (2007) has critiqued the application by the European Union of the generic FDA TTC to genotoxic impurities in pharmaceuticals as being too stringent because its derivation is biased by many classes of carcinogens of historic concern that would not be formed during pharmaceutical manufacture.

TTCs are similar in concept to the traditional TDI or ADI, and represent a level of exposure that is not of toxicological concern. Table 2-7 summarises some current regulatory uses of TTCs.

Table 2-7: Current uses of the threshold of toxicological concern (TTC)

Organisation	Use	References
US Food & Drug Administration (FDA)	*De minimus* level for regulation of minor contaminants (i.e. chemicals in food packaging materials that can migrate). TTC is applied as a threshold of regulation for indirect food additives. The FDA has dealt with 183 applications under this regulation and issued 78 exemptions using the TTC concept (Barlow 2005).	FDA (1993a, 1993b, 2006).
Joint FAO/WHO Expert Committee on Food Additives (JECFA)	Evaluation of flavouring substances Different TTCs for different structural classes have been used for the safety evaluation of over 1,200 flavouring substances (Barlow 2005).	JECFA (1993,1995,1999) Munro et al., (1999) Renwick (2004, 2005)
European Commission Scientific Committee on Food (SCF) [a]	Evaluation of flavouring substances	EFSA (2004b)
European Medicines Agency (EMEA)	Assessment of genotoxic impurities in pharmaceutical preparations. See also Dolan et al. (2005) and Delany (2007).	CHMP (2004)
European Commission, Joint Research Centre	The TTC principle has been endorsed as a mechanism for the regulation of chemicals under draft chemical legislation reforms being considered by the European Union.	EC JRC (2005)

[a] The SCF is now known as the European Food Safety Authority (EFSA).

In establishing TTCs for chemicals that are not carcinogens, an evaluation of toxicological databases undertaken for non-carcinogenic endpoints is used (Munro et al 1996, 1999; Kroes et al 2000, 2004). In these evaluations, some 900 non-carcinogenic organic chemicals were assigned to three 'classes' based on their chemical structure, presence of structural alerts for toxicity and known metabolic pathways, according to the classification scheme of Cramer et al (1978). The Cramer classification scheme divides chemicals into three classes according to their predicted toxicity as judged from structural alerts and metabolism:

- *Class I* are chemicals of simple structure with known metabolic pathways and innocuous end products that suggest a low order of toxicity.
- *Class II* contain chemical structures that are intermediate; they are chemicals that are less innocuous; they may contain reactive functional groups but do not contain the structural features suggestive of toxicity.
- *Class III* are chemicals for which structural features or likely metabolic pathways permit no strong presumption of safety, or may even suggest significant toxicity.

The 5th percentile NOEL of each of the three Cramer classes was divided by an uncertainty (safety) factor of 100 to yield TTC values that are somewhat higher than those created by the FDA for carcinogens. No formal stratification of toxicological end points was used in establishing NOAELs for the three Cramer chemical classes. The NOAELS are:

- *Class I* — 3 mg/kg/day (equates to a TTC of 30 µg/kg bw/day)
- *Class II* — 0.9 mg/kg/day (equates to a TTC of 9 µg/kg bw/day)
- *Class III* — 0.15 mg/kg/day (equates to a TTC of 1.5 µg/kg bw/day).

Renwick (2004, 2005) describes how JECFA applies the TTCs of the Cramer structural classes to the safety evaluation of flavouring agents. Since 1996, some 1200 chemical compounds have been assessed using the TTC concept.

The Expert Group of the Threshold for Toxicological Concern Task Force of the European branch of ILSI has examined the TTC principle. The experts were asked to address the question of whether neurotoxic, developmental, immunotoxic, allergenicity or endocrine activities could occur at low dose levels, and to explore whether there are reasons to assume that such endpoints may have thresholds below the proposed generic threshold of 0.02 µg/kg/day (Kroes et al 2000). The expert group also considered whether certain toxicological end points warranted separate structural 'classes', with TTCs different from those of the Cramer classes.

Within the limitation of the databases, developmental neurotoxicity and developmental toxicity were no more sensitive than other non specific endpoints. The cumulative distribution NOELs for these endpoints were similar to those for the chronic toxicity of the class III compounds of Munro et al (1996, 1999). Although data were relatively limited, it was also concluded that immunotoxicity was no more sensitive than other endpoints (Kroes et al 2000, 2004). The cumulative distribution of NOELs for neurotoxic compounds was lower than for other non cancer endpoints, suggesting this to be a more sensitive effect, the former was driven primarily by the organic phosphate esters and a biochemical response (inhibition of cholinesterase) rather than a toxicological response (Step 6c, below).

With the exception of a subclass of neurotoxicants, all these potential health effects are thus accommodated by the TTCs developed for the Cramer classes and the generic TTC established for genotoxic carcinogens. With regards to endocrine toxicity, the panel noted that miscellaneous estrogenic compounds of anthropogenic origin (excluding those specifically designed for endocrine activity) possess only low hormonal activity, and animal studies do not indicate that hormonal effects are expected from low concentrations in food. This is also likely to be the case for low concentrations of these chemicals in water. Because there were conservative assumptions at each step of data compilation and analysis, and 'worst case' perspectives were taken, the expert group concluded that intake at or below the TTCs provides an adequate safety assurance.

In this document, the Cramer classification has been performed using ToxTree, a software program released by the European Chemical Bureau (ECB) for this purpose. In assessing the suitability of the ToxTree software for classification of organic chemicals found in recycled water into the 'Cramer classes', all the compounds classified by Cramer et al (1978), Munro et al (1996) and Blackburn et al (2005) have been classified using ToxTree. Concordance was found between the software classifications and the manual classifications undertaken by experts and reported in the above publications. However, in some instances ToxTree did not produce clear classifications; these primarily relate to stereochemistry issues and are easily recognised in the output of ToxTree. Consequently, in Figure 2-1, at Step 6b, if there is a question regarding the possible reliability of the ToxTree classification, the default NOAEL to be applied to that substance is the 'generic' TTC of 0.02 µg/kg/day for genotoxic chemicals.

Safety factors used with NOEL of the TTC:
In Step 5d of Figure 2-1 the toxicological data base provides information on choice of safety factors to apply to the NOAEL or NOEL (NHMRC 1999; WHO 1990, 1994a, 1999). For chemicals that do not have any, or only extremely limited, toxicological data choosing safety factors with the aid of empirical information cannot be done. This dilemma has been overcome by using the NOEL for the TTC in Equation 1 and the 95th percentile of all the safety factors that have been applied by the NHMRC–NRMMC (1994) or WHO (2006) to NOAELs/NOELs of chemical compounds when they have set a drinking water guideline. This is more conservative than the common application of a 100 fold safety factor when using the TTC (eg Rodriguez et al 2007). The NHMRC/WHO 95th percentile safety factor is 1,500 (rounded from 1570 see Appendix 1, this means that for 95% of the chemical drinking water guidelines established by NHMRC/WHO the safety factor was less than 1500). Thus there is an additional safety factor of 15 that has been applied in converting the NOEL for a TTC to drinking water guidelines, as shown in Table 2-8.

Metals and dioxin-like substances are not represented in the databases used to establish the TTCs; therefore, these substances are not covered by the TTC concept at this time.

Step 6c— Is the chemical a cholinesterase inhibitor?
The cumulative distribution of NOELs for neurotoxic chemical compounds differs from the distribution of the NOELs for chronic toxicity for structural class III (Kroes et al 2000). Therefore, the expert group (Kroes et al 2004) examining the acceptability of the TTC values assigned to Cramer structural classes I, II, and III by Munro et al (1996) looked at whether neurotoxicants should be considered as a separate class for TTC application. The database used by Kroes et al (2000) and by Kroes and Kozianowski (2002) was biased towards high potency because most chemical compounds considered were organophosphates, and the 'toxicological' end point was based on inhibition of cholinesterase. The latter, especially inhibition of plasma cholinesterase, is arguably a biochemical marker rather than a functional alteration of physiology falling within the usual definition of an adverse effect used to establish a TDI.

Kroes et al (2004) investigated the effect of replacing the plasma cholinesterase inhibition with endpoints of neurotoxicological relevance. Their review found no clear relationship between brain, red blood cell, and plasma cholinesterase inhibition,[10] and concluded that organophosphates should be considered as a separate class of substances within the TTC framework. Furthermore:

- the cumulative distribution of organophosphates differed by one order of magnitude from the distribution of NOELs of neurotoxicants that are not organophosphates.
- the 5th percentile NOEL of 31 organophosphates was lower than the 5th percentile NOEL of Cramer structural class III compounds in the Munro et al (1996) database.

The 5th percentile NOEL for the organophosphates, divided by an uncertainty (safety) factor of 100, yields a TTC for organophosphates of 18 µg/person/day (0.3 µg/kg bw/day); non organophosphate neurotoxicity is adequately allowed for by the class III TTC (Munro et al 1996, 1999, Kroes et al 2000, 2004).

[10] 20% inhibition was taken as the level of toxicological significance for cholinesterase inhibition endpoints.

Table 2-8: Thresholds of toxicological concern (TTC) for Cramer structural chemical 'Classes' and certain toxicological endpoints, with corresponding DWG recommendation.

Chemical Class/ Toxicological endpoint	5th Percentile NOEL (mg/kg/d)	TTC (µg/kg/d)	Reference	Recommended DWG (µg/L)[e]
Structural Class I	3	30 [a]	Munro et al. 1996, 1999	7 or 14
Structural Class II	0.91	9 [a]	Munro et al. 1996, 1999	2 or 4
Structural Class III [b]	0.15	1.5 [a]	Munro et al. 1996, 1999	0.35 or 0.7
Developmental toxicity	3.46	34.6 [a]	Kroes et al. 2000, Kroes & Kozianowski 2002	8 or 16
Neurotoxicity (Cholinesterase inhibitors)	0.03 [c]	0.3 [a]	Kroes et al. 2000, Kroes & Kozianowski 2002	1 or 2
Genotoxic compounds	5th percentile associated with 10^{-6} carcinogenic risk	0.002 [d]	Kroes et al. 2004 Barlow 2005	0.007 or 0.014
Others	5th percentile associated with 10^{-6} carcinogenic risk	0.02 [f]	US FDA 1995 CFR 2001	0.07 or 0.14

NOEL = no observed effect level; TTC = threshold of toxicological concern

a Calculated by dividing the 5th percentile no observed effect level (NOEL) by a safety factor of 100. This is the TTC used by various authorities in assessing risks associated with minor contaminants in food.

b Substances whose structure or presumed metabolism permit no strong presumption of safety, or even suggest significant toxicity.

c This NOEL is driven by inhibition of cholinesterase by phosphate esters.

d Genotoxic compounds are assumed to potentially be carcinogens of high potency, consequently the TTC recommended by Kroes et al (2004) and Barlow (2005) is the value used to set a DWG, rather than the US FDA (1995) value as it embodies a more up-to-date assessment of an expanded database than was undertaken by the FDA. The recommended TTC is 0.15 µg/person/day (i.e. 0.002 µg/kg/d). The appropriate TTC, as mg/kg/d, is inserted into Equation 2 of Box 2-3 in lieu of the tolerable daily intake (TDI). Note genotoxic carcinogens with 'high cancer potency' structural alerts (aflatoxin-like compounds, N-nitroso-compounds and azoxy-compounds) are not covered by the TTC concept and require specific compound-related data for their evaluation.

e The recommended drinking water guideline is calculated by inserting the 5th percentile NOEL into Equation 1 (Box 2-4) and assuming P = 10% or 20%, depending on whether the chemical is likely to be in commercial use (10%), or not (20%), according to the Australian Inventory of Chemical Substances (ACIS). The safety factor used is 1500 (this is the 95th percentile value of safety factors used by the NHMRC-NRMMC [2004] or WHO [2006] on experimental NOELs, see text). The exception is for cholinesterase inhibitors; here the toxicological endpoint upon which the TTC is based is inhibition of blood cholinesterase. The human effect response associated with inhibition of blood cholinesterase is quite well defined; consequently, there is much less uncertainty associated with this group of compounds and a lower safety factor is appropriate. The safety factor applied is 100 (10 × for variability in response between humans and 10 × for extrapolation of animal experimental data to humans). Values in the table have been rounded.

f Compounds in this group are those with uncertain genotoxicity that cannot be classified into a Cramer class. In this situation the generic TTC of the US FDA (1995) is used in lieu of the TDI in Equation 2 of Box 2-3.

For this report, the recommended TTC for organophosphates was extended to cover all substances whose primary mode of toxicological action is inhibition of cholinesterase. Thus, for cholinesterase inhibiting substances for which no drinking water guideline existed, a TTC of 0.3 µg/kg/day was applied in Equation 2 of Box 2-4 to set a guideline.

Only three compounds in Table 2-11 were acetylcholine esterase inhibitors and did not have an assigned drinking water guideline. These were tri(dichlorisopropyl)phosphate, triphenyl phosphate and tris(2-chlorethyl)phosphate. Since all these substances are on AICS, they were presumed to be in commercial use; hence, 10% of the TTC for anticholinesterase compounds (0.3 µg/kg/day) was assigned to drinking water. The recommended drinking water guideline was therefore set at 1 µg/L as per Table 2-8.

Step 6d — Setting guideline values

Based on the classification of chemicals described in Steps 6a–6c, guideline values were derived using the approach and information summarised in Table 2-8. The resulting drinking water guidelines for non-pharmaceutical chemicals for which no suitable toxicological or health data was found are summarised in Table 2-9.

Table 2-9: Cramer classification of compounds without toxicological information that are not genotoxics, pharmaceuticals or cholinesterase inhibitors

Chemical name	Toxtree classification class	TTC (µg/kg bw/day) [a]	Recommended drinking water guideline (µg/L) [b]
Organic compounds			
Musks			
Musk tibetene	III	1.5	0.35 [b]
Pentamethyl-4,6-dinitroindane (Musk moskene)	III	1.5	0.35 [b]
Other compounds			
(Propylenedinitrilo)tetraacetic acid (PDTA)	III	1.5	0.7 [c]
1,7-Dimethylxanthine (Paraxanthine)	III	1.5	0.7 [c]
2,5-Dihydroxybenzoic acid	I	30	7 [b]
2,6-di-tert-butylphenol (2,6-bis(1,1-dimethylethyl)phenol)	II	9	2 [b]
4-Acetyl-6-t-butyl-1,1-dimethylindan	I	30	7 [b]
4-cumylphenol	III	1.5	0.35 [b]
6-Acetyl-1,1,2,4,4,7-hexamethyltetraline	II	9	4 [c]
Bromoacetic acid	III	1.5	0.35 [b]
Bromochloroacetonitrile	III	1.5	0.7 [c]
Caffeine	III	1.5	0.35 [b]
Chlorophene	III	1.5	0.35 [b]
Coprostanol (5beta-Cholestan-3beta-ol)	III	1.5	0.7 [c]
Diatrizoate sodium	III	1.5	0.35 [b]
Diatrizoic acid	III	1.5	0.35 [b]
Monobutyltin	III	1.5	0.7 [c]
Triclosan	III	1.5	0.35 [b]
Genotoxic compounds			
2,6-di-tert-butyl-1,4-benzoquinone (2,6-bis(1,1-dimethylethyl)-2,5-Cyclohexadiene-1,4-dione)	-	0.02	0.14 [c]
5-methyl-1H-benzotriazole	-	0.02	0.07 [b]
Cholinesterase inhibitors			
Fyrol FR 2 (tri(dichlorisopropyl) phosphate)	-	0.3	1 [b]
Triphenyl phosphate	-	0.3	1 [b]
Tris(2-chloroethyl)phosphate	-	0.3	1 [b]

TTC = threshold of toxicological concern

a TTC taken from Table 2-8.
b Likely to be in commercial use, P = 10%.
c Presumed not to be in commercial use, P = 20%.

2.2.7 Step 7 - Pharmaceuticals

Many of the chemicals of interest identified in Table 2-1 and Table 2-2 are active ingredients of pharmaceutical chemical compounds. In the human body, pharmaceuticals are generally metabolised and cleared as the parent compound and its metabolites. Excretion from the body is the primary source of pharmaceuticals in wastewater. Less commonly, pharmaceuticals may be introduced through industrial accidents and releases from hospitals or animal treatment facilities. Although raw waters may contain limited quantities of pharmaceuticals, it is unusual to find measurable concentrations in drinking water.

A regulatory framework for establishing guidelines for pharmaceutical chemicals in drinking water was not identified in developing these guidelines. The TTC approach is not required for pharmaceuticals as health data is available.

Active compounds of pharmaceutical products are arguably the most extensively examined chemicals, with clear definitions of toxicity and appropriate pharmacological doses. Because the biological activity (ie the therapeutic effect) of pharmaceuticals is so well defined, it is unusual for TDIs based on toxicity to be established for these chemicals. The exception is for pharmaceuticals used for agricultural and veterinary purposes where TDIs have been established by bodies such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) the Australian Therapeutics Goods Administration (TGA) and the European Agency for the Evaluation of Medicinal Products (EMEA). These TDIs have been used to determine guideline values.

The biological or pharmacological activity at therapeutic doses for pharmaceuticals used for humans is well known, and can be found in the manufacturer's literature and in various pharmacopoeias. The recommended therapeutic doses of pharmaceuticals are intended to elicit a biological outcome in patients. However, the ratio of doses causing toxicity to the doses giving a beneficial effect (the therapeutic index) is intended to be large[11]. Hence, to establish a drinking water guideline for a pharmaceutical chemical, the approach is to divide the recommended therapeutic dose by a safety factor that would provide reasonable assurance that effects, either pharmacological or toxic, would be unlikely. Toxicological profiles of pharmaceuticals indicate that none will have a therapeutic or other biological effect at daily doses a hundredfold less than the lowest therapeutic dose. This approach has been applied by Schwab et al (2005) in a human health risk assessment of pharmaceuticals in United States surface waters and by Versteegh et al (2007). DEFRA (2007) also used the lowest therapeutic dose as the basis for assessing the risk from pharmaceuticals in drinking water.

Dolan et al (2005) took a different approach to assessing the risk of pharmaceuticals in environmental media. The authors reviewed ADI values derived since 1981 for active pharmaceutical ingredients of the Merck pharmaceutical company. The analysis excluded genotoxic compounds. The database consisted of 120 chemical compounds, with a broad range of potencies that are administered orally or parenterally. The study found that 94% of the compounds with known pharmacological activity had ADIs[12] greater than 10 µg/day (i.e. 0.15 µg/kg/day); this ADI applied to Equation 2 of Box 2-4 would result in a drinking water guideline of 5 µg/L.

The approach adopted in this report is to calculate surrogate TDIs (S-TDIs) for pharmaceutical agents by dividing the lowest recommended therapeutic dose (as mg/kg/day) by safety factors.

[11] Many of the pharmaceutical compounds in Table 2-1 and Table 2-2 are nonsteroidal anti-inflammatory agents, antibiotics, or beta-blockers. These agents would be expected to have a therapeutic index of much more than 10 fold.
[12] Dolan et al (2005) do not provide the basis of the ADIs (ie whether set on pharmacological or toxic NOEL) or the magnitude of the uncertainty factor applied to the NOEL.

Setting safety factors for pharmaceuticals

It is standard practice to apply safety (or uncertainty) factors to derive guideline values from base data for threshold chemicals (in this case lowest recommended therapeutic doses) that are designed to be protective of human health. The Australian Drinking Water Guidelines (NHMRC–NRMMC, 2004) uses the term safety factor while WHO (2006) uses the term uncertainty factor. Ritter et al (2007) have reviewed these factors and their application by WHO and by Australia, Canada and the United States. Safety factors described in the Australian Drinking Water Guidelines (NHMRC–NRMMC 2004) are as follows:

- *Interspecies variation* — a factor of 10 is applied to account for uncertainty when extrapolating from studies on experimental animals to humans.
- *Intraspecies variation* — a factor of 10 is applied to take account of variations within humans.
- *Subchronic to chronic* — a factor of 10 is applied if data from a subchronic study is used in the absence of reliable data from chronic studies (this factor can be less if chronic studies are available and indicate that no other effects occur, or that other effects are mild).
- *Lowest observed effect level (LOEL) versus NOEL* — a factor of up to 10 is applied if effects have been observed at the lowest doses (guidelines are preferably derived from the highest dose at which no adverse effects are seen).

Other safety factors have been described for data base uncertainty (1–10), protection of infants and children (1–10) and nature or severity of effect. Individual safety factors lower than 10 can be applied where there is sufficient information to justify a reduction. This can include information on mechanisms of action, human epidemiological data and evidence that adverse effects are relatively minor. The rationale for using safety factors between 1 and 10 are discussed in Ritter et al (2007). In deriving guideline values for pharmaceuticals, Schwab et al (2005) applied safety factors for LOEL to NOEL, subchronic to chronic, interspecies variation, intraspecies variation and database uncertainty. In a number of cases, safety factors of 2–5 were used rather than 10.

While application of safety factors are entrenched in international guideline setting practices, application is influenced by subjective judgments. Nonetheless, there is a degree of consistency in the magnitude of total or composite safety. There is general agreement that the total safety factor should not exceed 10 000 and this convention is applied by Health Canada, WHO, US EPA and NHMRC. The US EPA uses an upper limit of 10 000 to avoid overlap and overprotection associated with higher safety factors (Dourson et al 1996, Ritter et al 2007).

As shown in Section 6, the 50th and 95th percentiles of safety factors used in deriving guideline values from NOELs in the Australian Drinking Water Guidelines (NHMRC–NRMMC, 2004) are 270 and 1570 respectively, and in the WHO Guidelines (WHO 2006) are similar at 170 and 1660 respectively. About 90% of safety factors applied in drinking water guidelines are 1000 or less. Schwab et al (2005) applied safety factors ranging from 9 to 200 to the lowest daily therapeutic dose for 26 pharmaceuticals (50th percentile 90). An additional safety margin was applied by using child body weights of 14 kg and consumption of 1 L per day (compared to adult body weights of 70 kg and consumption of 2 L per day). In effect this adds a further margin of 2.5, meaning that total safety factors of 22.5 to 500 were applied (50th percentile 225).

Versteegh et al (2007) derived guideline values for pharmaceuticals using the lowest pharmacologically effective dose, a safety factor of 100, a body weight of 60 kg and consumption of 2L per day.

DEFRA (2007) applied a safety margin of 1000.

In this publication, the following safety factors have been applied:

- *all pharmaceuticals* — a safety factor of 1000 is applied, comprising
  - 10 for differences in response between humans including sensitive individuals (intraspecies variation)
  - 10 for protection of sensitive subgroups including children and infants
  - 10 for the lowest daily therapeutic dose not being a no-effect level
- *cytotoxic drugs* — an additional safety factor of 10 is applied due to the higher level of toxicity associated with these compounds
- *hormonally active steroids* — an additional safety factor of 10 is applied, on the grounds that potential effects on hormonal function and fertility is unwanted in those not being treated.

This means that the safety factors applied to pharmaceuticals range from 1000 to the maximum applied in all drinking water guidelines of 10 000. Considering that a safety factor is not required for interspecies variation, this is considered to be a conservative approach. The combined factor of 100 for intraspecies variability and protection of sensitive subgroups is considered to be adequately address issues associated with potential exposure of infants, children and those with allergies or other contraindications. Specific health risks for children and infants has been the subject of some discussion (WHO 2006, US EPA 2006) but there is no consistent approach for applying safety factors to infants or other sensitive subgroups. Application of an additional safety factor of 10 is considered a conservative approach. The United States Food Quality Protection Act (US 1996) applies a default safety factor of 10 in dealing with pesticides in food products.

There is limited information on allergic reactions that can be used in modifying guideline values. The guideline value for the penicillins is based on preventing allergic reactions (EMEA 2005). This value has been applied to all β-lactams.

Proportion allocated to water

Based on the rationale that pharmaceutical chemicals are not widespread in the environment or likely to be present in food, the proportion of the S-TDI allocated to water for pharmaceuticals is 100%. For persons taking medication, intake of a pharmaceutical chemical at the recommended drinking water guideline determined using this methodology (shown in Box 2-7) will be an additional 0.1% of their daily dose, or 0.01% for cytotoxic drugs or steroidal hormones. At these very low concentrations no effect is anticipated from there being potentially a number of similar pharmaceuticals in the drinking water as the combined dose will still be significantly less than that associated with either a therapeutic or toxic effect.

For pharmaceuticals with agricultural or veterinary use the proportion allocated to water is 10%.

An example of the recommended approach can be seen with norfloxacin, which has been found at concentrations of up to 7 µg/L in wastewater. The lowest recommended daily dose in two parts is 800 mg (ie 400 mg every 12 hours). For a 70 kg adult, that represents a dose of 11.4 mg/kg/day. Applying the above rules, this would mean that water concentrations of norfloxacin should not exceed 4000 µg/L, which is substantially in excess of the concentration of 7 µg/L measured in wastewater. A similar process can be applied to any pharmaceutical. Because of the continuous introduction of new pharmaceuticals to the pharmacopoeia, any listing of the lowest doses of pharmaceuticals already available would rapidly lose currency. Given these circumstances, it is better to identify the pharmaceutical chemical in the water supply and thereafter apply these

principles to the concentrations found. This process will be effective irrespective of the origin of pharmaceutical (eg appropriate therapeutic use, hospital discharge or inadvertent release into water bodies).

Box 2-7: Calculation of drinking water guidelines using therapeutic doses

$$\text{Drinking water guideline } (\mu g/L) = \frac{\text{S-TDI (mg/kg/day)} \times \text{bw (kg)} \times P \times 10^3}{V \text{ (L/day)}} \quad \text{..... Equation 4}$$

Where:

S-TDI = surrogate-TDI (mg/kg/day) = LTD (mg/person/d) ÷ [SF (1,000 or 10,000) x bw (kg)]
P = proportion of S-TDI from water = 100% if a human pharmaceutical but 10% if used in agricultural or veterinary practice.
bw = bodyweight (70kg)
V = volume of water drunk (2L/day)
10^3 = unit conversion mg/L to µg/L.

If using the lowest therapeutic dose directly instead of the S-TDI, Equation 4 becomes:

$$\text{Drinking water guideline } (\mu g/L) = \frac{\text{LTD (mg/day)} \times P \times 10^3}{SF \times V \text{ (L/day)}} \quad \text{..... Equation 4a}$$

Where:

LTD = lowest daily oral therapeutic dose for an adult. The LTD is taken from (in order of priority) MIMS, Martindale, or another pharmacopeia for preparations that have the chemical as a sole ingredient. If dose information is not available for the single agent, then doses from combination preparations are used. If an LTD cannot be located, then either the LTD for a similar active ingredient can be used with an extra safety factor of 10, or a TTC can be derived using a Cramer classification.

SF = safety factor; 1,000 for most pharmaceuticals, 10,000 for cytotoxic chemical compounds and 10,000 for synthetic or natural hormones.

Table 2-10 presents calculated drinking water guidelines for the pharmaceutical chemicals identified in Table 2-1 and Table 2-2 and compares them with the highest concentrations measured in secondary treated effluent. With limited exceptions the margins of exposure resulting from this comparison are greater than 1 with many being a 1000 or more. Given that this does not take into account reductions achieved by advanced treatment processes, it is unlikely that pharmaceutical chemicals will be present at levels approaching the recommended drinking water guideline, or cause any untoward effects in people drinking water augmented with recycled water.

The exceptions are alprazolam, valium, the estrogenic hormones and the antibiotics amoxicillin, chlorotetracycline and monensin. The concentrations of each of these chemical compounds would be reduced to below guideline values by advanced treatments, including reverse osmosis (Ternes and Joss 2006, Costanzo and Watkinson 2007, Snyder et al 2007). Removal of estrogenic hormones has been demonstrated in a number of studies (Huang and Sedlak 2001, Khan and Roser 2007). Testing of recycled water produced at the Orange County Groundwater Replenishment Scheme (Daugherty et al 2005) and the Singapore NEWater Scheme[13] has not detected 17α-ethynylestradiol, estrone or 17β-estradiol.

[13] http://www.pub.gov.sg/NEWater_files/download/review.pdf

Table 2-10: Recommended drinking water guideline for pharmaceuticals*

Pharmaceutical	Highest effluent conc (µg/L)	LTD (mg/day) or ADI (µg/kg/day) [a]	Recommended drinking water guideline (µg/L)	Margin of exposure (DWG ÷ highest conc)
Antibiotics				
Amoxycillin	5	ADI 0.43 [f]	1.5	0.3
Anhydro-erythromycin A	0.92	5[o]	17.5 [c]	10
Azithromycin	0.072	ADI 11 [o]	4	54
Cefaclor	1.21	500	250	200
Cephalexin	0.09	ADI 10 [b]	35	390
Chloramphenicol	23	3,500	175 [q]	7.6
Chlortetracycline	160	ADI 30 [g]	105	0.65
Ciprofloxacin	0.03	500	250	8,300
Clarithromycin	0.24	500	250	1,040
Clindamycin	0.120	600	300	2,500
Demeclocycline	1.12	600	300	270
Doxycycline	0.03	ADI 3 [e]	10.5	350
Enrofloxacin	0.002	ADI 6.2 [e]	22	11,000
Erythromycin	1.7	ADI 5 [e]	17.5	10
Lincomycin	0.015	ADI 1,000 [b]	3,500	230,000
Monensin	80	ADI 10 [b]	35	0.44
Naladixic acid	0.22	2,000	1,000	4,550
Norfloxacin	7	800	400	57
Oxytetracycline (Terramycin)	0.34	ADI 30 [g]	105	310
Penicillin G	0.03	ADI 0.43 [f]	1.5	50
Penicillin V	0.21	ADI 0.43 [f]	1.5	7
Roxithromycin	460	300	150	0.3
Sulfadimethoxine	0.06	ADI 10 [p]	35	580
Sulfamethazine	0.22	ADI 10 [p]	35	160
Sulfamethiazole	0.13	ADI 10 [p]	35	270
Sulfamethoxazole	94	ADI 10 [p]	35	0.4
Tetracycline	0.11	ADI 30 [g]	105	950
Trimethoprim	0.35	ADI 20 [b]	70	200
Tylosin	5	ADI 300 [b]	1,050	210
Nonsteroidal anti-inflammatory drugs (NSAIDs)				
Aspirin	2.1	ADI 8.3 [e]	29	14
Diclofenac	0.81	ADI 0.5 [e]	1.8	2.2
Dipyrone	7.5	ADI 150[e]	525	70
Fenoprofen	0.759	900	450	590
Ibuprofen	28	800	400	14
Indomethacin	0.6	50	25	14
Ketoprofen	0.38	ADI 1 [b]	3.5	9
Naproxen	0.57	440	220	380
Tolfenamic acid	1.6	ADI 5 [b]	17.5	11
β-andrenergic blockers				
Betaxolol	0.19	20	10	53
Bisoprolol	0.37	1.25	0.6	1.7
Carazolol	0.12	ADI 0.1 [h]	0.35	2.9
Metoprolol	2.2	50	25	11
Nadolol	0.06	40	20	330
Propranolol	0.29	80	40	140

Pharmaceutical	Highest effluent conc (µg/L)	LTD (mg/day) or ADI (µg/kg/day) [a]	Recommended drinking water guideline (µg/L)	Margin of exposure (DWG ÷ highest conc)
Timolol	0.07	20	10	140
Estrogenic compounds [d]				
17α-ethinyl estradiol	0.062	0.03	0.0015[d]	0.24
17α-estradiol	0.074	-	0.175 [d,j]	2.4
17β-estradiol	0.027	ADI 0.05 [i]	0.175[d]	6.5
Equilenin (horse steroid)	0.278	0.6	0.03[d]	0.11
Equilin	0.15	0.6	0.03[d]	0.2
Estriol	0.051	1	0.05[d]	1
Estrone	0.7	0.6	0.03[d]	0.04
Mestranol	0.407	0.05	0.0025[d]	0.006
Norethindrone	0.872	5	0.25[d]	0.29
Progesterone	0.199	ADI 30 [i]	105[d]	530
Androgenic compounds [d]				
Androsterone	0.214	-	14 [k]	65
Testosterone	0.214	ADI 2 [i]	7	33
Other pharmaceuticals				
Acetaminophen (paracetamol)	4.3	ADI 50 [e]	175	41
Alprazolam	0.62	0.5	0.25	0.4
Antipyrine	0.41	2,000	1,000	2,400
Atorvastatin	0.044	10	5	110
Bezafibrate (Benzafibrate)	4.6	600	300	65
Carbamazepine	27.3	200	100	3.7
Cimetidine	0.58	400	200	340
Clenbuterol	0.05	ADI 4.2 [h]	15	300
Clofibric acid (Clofibrate)	1.6	1,500	750	470
Codeine	9.1	100	50	5.5
Cotinine ((S)-1-methyl-5-(3-pyridinyl) 2-Pyrrolidinone) [l]	0.9	20 [e]	10	11
Cyclophosphamide	0.02	70	3.5 [d]	175
Dehydronifedipine [m]	0.03	40	20	670
Diazepam	2.92	5	2.5	0.9
Diltiazem	0.049	120	60	1,220
Enalaprilat	0.046	2.5	1.3	27
Fluoxetine	0.012	20	10	830
Gemfibrozil	0.42	1,200	600	1,430
Iohexol	1.6	1,440	720	450
Iopamidol	1.6	800	400	250
Iopromide	1.8	1,500	750	420
Isophosphamide[n]	2.9	70	3.5 [d]	1.2
Metformin	0.15	500	250	1,670
Methotrexate	1	0.1	0.005 [d]	0.005
Salbutamol	0.035	6	3	86
Salicylic acid	2.1	Topical preps only. Cramer class 1	105	50
Stigmastanol	4	2,000	1,000	250
Sulfasalazine	0.12	1,000	500	4,170
Temazepam	1.64	10	5	3
Terbutaline	0.12	9	4.5	38

***** Values have been rounded.
a ADI's used for veterinary drugs as published by EMEA, WHO or TGA
b TGA (2006).
c Similar pharmaceutical, composite safety factor of 1,000.
d Cytotoxic or genotoxic agent, or steroid hormone, composite safety factor of 10,000.
e EMEA (various dates). The European Agency for the Evaluation of Medicinal Products. Veterinary Medicines Evaluation Unit.
f The maximum permitted daily intake of 30 µg parent compound per person (0.43 µg/kg bw/day), is agreed for penicillins in relation to the prevention of allergic reactions (EMEA 2005). This is also applied for amoxycillin.
g An ADI of 30 µg/kg bw/day was established for the tetracyclines (oxytetracycline, chlortetracycline and tetracycline) alone or in combination (WHO/JECFA 1998).
h Although an ADI for this compound has been published by the WHO, the EMEA published ADI value has been sourced on the basis that the EMEA report is a more recent evaluation.
i WHO/JECFA 2000
j Assumed same potency as 17β-estradiol.
k Androsterone is a weak androgen; here it is assumed to be 50% of testosterone potency.
l Cotinine is major metabolite of nicotine, rapidly cleared by the kidneys. Less active than nicotine which is given in antismoking regimes from about 10 mg/person (transdermal). Assume 50% activity of nicotine gives 20 mg/person for cotinine.
m Dihydronifedipine is the predominant metabolite of nifedipine. Minimal dose of nifedipine is 20 mg/day; assume 50% activity for the metabolite yields 40 mg/person.
n Isomer of cyclophosphamide
o Azithromycin is a chemically closely related parent compound of tulathromycin. A toxicological ADI of 11 µg/kg bw/d has been adopted for azithromycin and applies to tulathromycin, based on a 3-month subchronic toxicity study in dogs and rats and a safety factor of 100 (EMEA 2004a). An additional safety factor of 10 has been used in the calculation of a DWG for azithromycin on the basis that the ADI from a closely related compound (tulathromycin) was used. Anhydro-erythromycin A is a derivative of erythromycin, and the ADI of 5 µg/kg bw/d adopted for erythromycin has been applied (EMEA 2000).
p A guideline for sulphonamides in drinking water made from recycled water has been established herein by applying the lowest ADI for sulphonamides established by the NRA (i.e. 0.01 mg/kg bw/d [NRA 2000]). It is recommended that this be applied to all individual sulphonamides.
q Safety factor of 10,000 applied due to concerns of potential carcinogenicity.

2.3 Summary of recommended drinking water guidelines

The recommended DWGs established in the preceding sections are consolidated and summarised in Table 2-11.

Table 2-11: Summary of recommended DWG for chemicals in drinking water augmented with recycled water.

Chemical Name*	Recommended DWG (µg/L)	Chemical Name*	Recommended DWG (µg/L)
1,1-Dichloroethene (11DCE; 1,1-Dichloroethylene)	**30** [a]	4-Methylphenol (p-Cresol)	**600** [f]
1,7-Dimethylxanthine (Paraxanthine)	**0.7** [i]	4-Nitrophenol	**30** [f]
17α-estradiol	**0.175** [d]	4-Nonylphenol (4NP)	**500** [g]
17α-ethynylestradiol	**0.0015** [d]	4-tert-octylphenol	**50** [g]
17β-estradiol	**0.175** [d]	5-methyl-1H-benzotriazole	**0.007** [h]
2-(p-Chlorophenoxy)-2-methylpropionic acid (Clofibric acid)	**750** [d]	6-Acetyl-1,1,2,4,4,7-hexamethyltetraline	**4** [i]
2,3,3',4,4',5-Hexachlorobiphenyl (PCB156)	**16 pq TEQ/L** [f]	Acetophenone	**400** [f]
2,3,3',4,4'-pentachlorobiphenyl (PCB105)	**16 pq TEQ/L** [f]	Alachlor	**2** [b]
2,3',4,4',5-Pentachlorobiphenyl (PCB118)	**16 pq TEQ/L** [f]	α-BHC (alpha-BHC; alpha-lindane)	**20** [b]
2,4,5,3',4',5'-Hexachlorobiphenyl (PCB167)	**16 pq TEQ/L** [f]	Alpha particles	**0.5 Bq/L** [a]
2,4,6-Trichlorophenol (2,4,6-T)	**20** [a]	Alprazolam	**0.25** [d]
2,4,6-Trinitro-1,3-dimethyl-5-tert-butylbenzene (musk xylene)	**350** [g]	Amoxycillin	**1.5** [d]
2,4-D (2,4-Dichlorophenoxyacetic acid)	**30** [a]	Androsterone	**14** [d]
2,4-Dichlorophenol	**200** [a]	Anhydroerythromycin A	**10** [d]
2,5-Dihydroxybenzoic acid	**7** [i]	Anthracene	**150** [f]
2,6-Dichlorophenol	**10** [f]	Antimony	**3** [a]
2,6-di-tert-butyl-1,4-benzoquinone (2,6-bis(1,1-dimethylethyl)-2,5-Cyclohexadiene-1,4-dione)	**0.014** [h]	Antipyrine	**1,000** [d]
2,6-di-tert-butylphenol (2,6-bis(1,1-dimethylethyl)phenol)	**2** [i]	Arsenic	**7** [a]
2-Chlorophenol	**300** [a]	Aspirin (acetylsalicylic acid)	**30** [d]
2-Phenylphenol	**1,000** [b]	Atorvastatin	**5** [d]
3,4,5,3',4',5'-Hexachlorobiphenyl (PCB169)	**16 pq TEQ/L** [f]	Atrazine	**40** [a]
4,4'-DDE	**20** [b]	Azinphos-methyl	**3** [a]
4,4'-DDT	**20** [a]	Azithromycin	**4** [d]
4-Acetyl-6-t-butyl-1,1-dimethylindan	**7** [i]	Barium	**700** [a]
4-Chlorophenol	**10** [f]	Benzo(a)pyrene	**0.01** [b]
4-Cumylphenol	**0.35** [i]	Benzyl chloride	**0.2** [e]

Chemical Name*	Recommended DWG (µg/L)	Chemical Name*	Recommended DWG (µg/L)
β-BHC (beta-BHC; beta-lindane)	**20** [b]	Cotinine ((S)-1-methyl-5-(3-pyridinyl)-2-Pyrrolidinone)	**10** [d]
Beta particles & photon emitters	**0.5 Bq/L** [a]	Coumarin	**0.5** [a]
Betaxolol	**10** [d]	Cyclophosphamide	**3.5** [d]
Bezafibrate (Benzafibrate)	**300** [d]	Cypermethrin	**175** [f]
Bisoprolol	**0.6** [d]	Dehydronifedipine	**20** [d]
Bisphenol A	**200** [f]	Demeclocycline	**300** [d]
Boron	**4,000** [a]	Demeton-S	**0.15** [f]
Bromide	**7,000** [f]	Diatrizoate sodium	**0.35** [i]
Bromine	**7,000** [f]	Diatrizoic acid	**0.35** [i]
Bromoacetic acid	**0.35** [i]	Diazepam	**2.5** [d]
Bromochloroacetonitrile	**0.7** [i]	Diazinon	**3** [a]
Bromochloromethane	**40** [f]	Dibromochloromethane	**100** [a]
Bromodichloromethane	**6** [a]	Dibutyltin	**2** [f]
Bromoform	**100** [a]	Dichloroacetic Acid	**100** [a]
Bromophos-ethyl	**10** [a]	Dichloroacetonitrile	**2** [a]
Butylated hydroxyanisole (3-tert-butyl-4-hydroxy anisole)	**1,750** [f]	Dichloromethane (Methylene chloride)	**4** [a]
Butylated hydroxytoluene (2,6-Di-tert-Butyl-p-Cresol)	**1,000** [f]	Dichlorvos	**1** [a]
Cadmium	**2** [a]	Diclofenac	**2** [d]
Caffeine	**0.35** [i]	Diltiazem	**60** [d]
Carazolol	**0.35** [d]	Dimethoate	**6** [a]
Carbamazepine	**100** [d]	Di-n-butyl phthalate	**35** [f]
Carbendazim	**100** [a]	Dioxin like compounds (Total)	**16 pq TEQ/L** [f]
Cefaclor	**250** [d]	Diuron	**30** [a]
Cephalexin	**35** [d]	Doxycycline	**10.5** [d]
Chlordane	**1** [a]	Enalaprilat	**1.3** [d]
Chlorine	**5,000** [a]	Endosulfan sulfate	**30** [a]
Chloramphenicol	**175** [d]	Enrofloxacin	**22** [d]
Chloroform	**200** [a]	Equilenin	**0.03** [d]
Chlorophene	**0.35** [i]	Equilin	**0.03** [d]
Chlortetracycline	**105** [d]	Erythromycin	**17.5** [d]
Chlorpyrifos	**10** [a]	Estriol	**0.05** [d]
Chlorpyrifos-methyl	**10** [a]	Estrone	**0.03** [d]
Chromium	**50** [a]	Ethion	**3** [a]
Cimetidine	**200** [d]	Ethoprophos (Mocap)	**1** [a]
Ciprofloxacin	**250** [d]	Ethylenediaminetetraacetic acid (EDTA)	**250** [a]
Clarithromycin	**250** [d]	Fenoprofen	**450** [d]
Clenbuterol	**15** [d]	Fenthion (fenthion-methyl)	**0.5** [a]
Clindamycin	**300** [d]	Fluoranthene	**4** [b]
Codeine	**50** [d]	Fluoride	**1,500** [a]
Copper	**2,000** [a]	Fluoxetine	**10** [d]
Coprostanol (5beta-Cholestan-3beta-ol)	**0.7** [i]	Fyrol FR 2 (tri(dichlorisopropyl) phosphate)	**1** [c]

Chemical Name*	Recommended DWG (µg/L)	Chemical Name*	Recommended DWG (µg/L)
Galaxolide	**1,750** [g]	Norfloxacin	**400** [d]
Gemfibrozil	**600** [d]	Octachlorodibenzo-p-dioxin	**16 pq TEQ/L** [f]
Ibuprofen	**400** [d]	Oxytetracycline	**105** [d]
Indomethacin	**25** [d]	Paracetamol	**175** [d]
Iodine	**60** [f]	Parathion (ethyl parathion)	**10** [a]
Iohexol	**700** [d]	Parathion-methyl (Methyl parathion)	**100** [a]
Iopamidol	**400** [d]	PCBs (total)	**0.14** [a]
Iopromide	**750** [d]	Penicillin G	**1.5** [d]
Isophosphamide	**3.5** [d]	Penicillin V	**1.5** [d]
Ketoprofen	**3.5** [d]	Pentachlorophenol (PCP)	**10** [a]
Lead	**10** [a]	Pentamethyl-4,6-dinitroindane (Musk moskene)	**0.35** [i]
Lincomycin	**3,500** [d]	Pentetic acid	**250** [a]
Lindane	**20** [b]	Phenanthrene	**150** [f]
Malathion	**900** [a]	Phenol	**150** [f]
Manganese	**500** [a]	Phthalic anhydride	**7,000** [f]
Mestranol	**0.0025** [d]	Progesterone	**105** [d]
Metformin (1,1-dimethylbiguanide)	**250** [d]	Propranolol	**40** [d]
Methotrexate	**0.005** [d]	(Propylenedinitrilo) tetraacetic acid (PDTA)	**0.7** [i]
Metolachlor	**300** [a]	Pyrene	**150** [f]
Metoprolol	**25** [d]	Roxithromycin	**150** [d]
Molybdenum	**50** [a]	Salbutamol	**3** [d]
Monensin	**35** [d]	Salicylic acid	**100** [d]
Monobutyltin (MBT)	**0.7** [i]	Selenium	**10** [a]
Musk ketone	**350** [g]	Silver	**100** [b]
Musk tibetene	**0.35** [i]	Simazine	**20** [a]
N,N-diethyltoluamide (N,N-diethyl-3-methylbenzamide) (DEET)	**2,500** [g]	Stigmastanol	**1,000** [d]
Nadolol	**20** [d]	Sulfadimethoxine (SDMX)	**35** [d]
Nalidixic acid (Negram, Naladixic acid)	**1,000** [d]	Sulfamethazine (SMTZ)	**35** [d]
Naphthalene	**70** [f]	Sulfamethizole	**35** [d]
Naproxen	**220** [d]	Sulfamethoxazole	**35** [d]
Nickel	**20** [a]	Sulfasalazine	**500** [d]
Nitrate (NO_3^-)	**50,000** [a]	Sulfathiazole	**35** [d]
Nitrilotriacetic acid (NTA)	**200** [a]	Temazepam	**5** [d]
Nitrite (NO2)	**3,000** [a]	Terbutaline	**5** [d]
N-Nitrosodiethylamine	**0.01** [a]	Testosterone	**7** [d]
N-Nitrosodimethylamine	**0.01** [a]	Tetracycline	**105** [d]
N-nitrosomorpholine	**0.001** [e]	Thiophanate	**5** [a]
Nonylphenol	**500** [g]	Timolol	**10** [d]
Norethindrone	**0.25** [d]	Tolfenamic acid	**17.5** [d]

Chemical Name*	Recommended DWG (µg/L)	Chemical Name*	Recommended DWG (µg/L)
Tri(butyl cellosolve) phosphate (ethanol,2-butoxy-phosphate)	**50** [g]	Trimethoprim	**70** [d]
Tributyl phosphate	**0.5** [a]	Triphenyl Phosphate	**1** [c]
Tributyltin	**1** [b]	Tris(2-chloroethyl)phosphate	**1** [c]
Trichloroacetic acid	**100** [a]	Tylosin	**1,050** [d]
Triclosan	**0.35** [i]	Vanadium	**50** [a]
Trifluralin	**50** [a]		

* See Appendix 2 for Chemical Abstracts Service Registry Number (CASRN).
[a] From Table 2-1 (chemicals from Australian waters).
[b] From Table 2-2 (chemicals from overseas waters).
[c] Identified as acetyl cholinesterase inhibitor (Table 2-8).
[d] From Table 2-10 (pharmaceuticals).
[e] From Table 2-5 (non-threshold chemicals)
[f] From Table 2-3 (ADIs).
[g] From Table 2-4 (NOELs).
[h] Identified as probably genotoxic (see Table 2-8).
[i] From Table 2-9 (Threshold of toxicological concern).

SECTION 3 Source control and efficacy of treatment

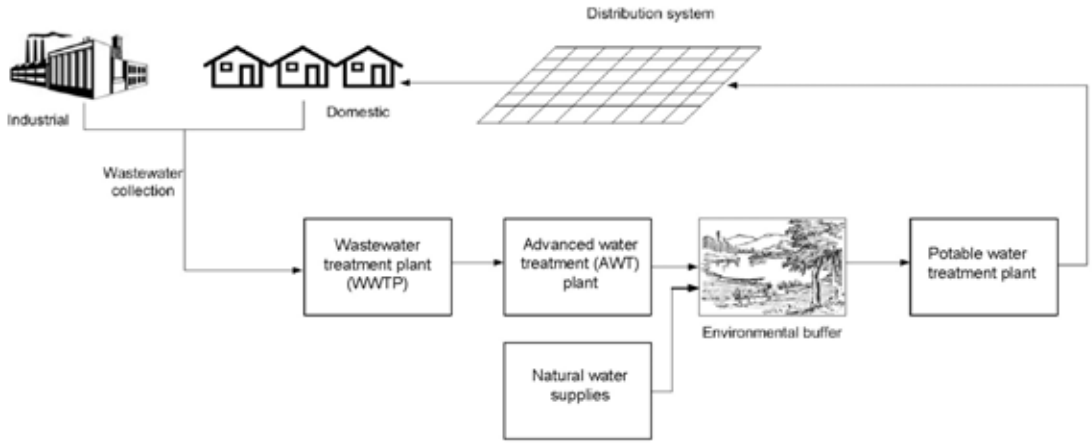
3.1 Introduction

Indirect Potable Recycling (IPR) projects, such as the Singapore NEWater program (Seah et al. 2003), the Orange County Groundwater Replenishment system (Daugherty et al. 2005) or Queensland's Western Corridor Recycled Water Project, are built on a combination of "treatment barriers" that control the concentrations of hazardous substances and "preventative measures" that control exposure to hazards. The overall IPR process begins with a source control (or trade waste) program and concludes with the operation and maintenance of the drinking water distribution system (Figure 3-1). Individual treatment technologies used in the wastewater treatment plant, advanced water treatment plant, and the drinking water treatment plant are referred to as "treatment barriers", whereas preventative measures include the execution of the trade waste program, management of the environmental buffer, and maintenance of the distribution system. The following chapter presents information on the efficacy of the various "preventative measures" and "process barriers" that are used to reduce or eliminate the concentration of a suite of chemicals that are present, or have the potential to be present, in the source water (i.e. recycled water) for IPR projects.

3.1.1 Features of indirect potable reuse schemes

IPR refers to the practice of the planned addition of highly treated wastewater (i.e. recycled water) into either surface water or groundwater that is then used to augment a drinking water supply. An IPR scheme consists of the following components (Figure 3-1).

Figure 3-1: Elements of an indirect potable reuse scheme.



The components of the IPR scheme as depicted in Figure 3-1 are:

- A sewage collection system which incorporates a rigorous trade waste policy that regulates the discharge of wastewater from industry.
- A wastewater treatment process that minimizes and removes a range of chemical and soluble nutrients so that the wastewater can be discharged to the environment.
- A sewage treatment process that provides some degree of disinfection.
- An advanced treatment process that recovers water that would have otherwise been lost to the environment.

- A pumping and conveyance system that delivers recycled water to surface water or groundwater storage to augment the overall raw drinking water supplies.
- A drinking water treatment plant that treats raw water prior to delivery to homes and industry though a drinking water distribution network.

The overarching design intent of the indirect potable reuse system is to reduce/remove the potential of public exposure via the potable water distribution system of those chronic and acute risk factors that originate in the untreated wastewater. The design intent is achieved by ensuring that the series of barriers collectively reduce/remove the concentration of risk factors to less than the tolerable levels defined by the guidelines regulating both recycled and drinking water supplies.

3.1.2 Concept of multiple barriers and definition of barriers in context of NHMRC guidelines

The process of reducing the concentration of any element, chemical compound, macromolecule, colloid, particle or microorganism by the application of individual treatment technologies in series is referred to as the "multiple barrier" approach to water treatment. The phrase "multiple barriers" was introduced in 1970 to describe the series of treatment steps to reduce the concentration of microbial pathogens in a wastewater treatment process, where the receiving water was used as part of the water supply (Velz 1970). The concept of multiple barriers has now been extended in the most recent draft of the California Department of Public Health's guidelines for groundwater recharge with reclaimed water to include organic chemicals (CDPH 2007). There is, however, an implicit expectation that the performance criteria for "multiple barriers" will be different for microorganism compared to chemicals. In the case of microorganisms, the performance expectation mirrors the requirements for drinking water systems, where the overall treatment objective for the reduction of microorganisms (such as viruses) will be achieved even if a single treatment barrier fails (NRC 1998). In the case of chemicals, the expectation is that a series of treatment steps will be used to reduce the overall chemical load (measured as total organic carbon). Recent regulations promulgated in California make provisions for multiple barriers for chemicals such as an advanced oxidation process in conjunction with reverse osmosis to reduce the concentration of a regulated chemicals such as NDMA or 1,4-dioxane. However, the requirements for redundancy normally associated with microbial removal are not applied to the multiple barriers for chemicals. This is because exposure to chemicals is more of a chronic risk, relating to long-term exposure, compared with the acute risks associated with viruses, bacteria and protozoa, for which even short term exposure may have significant impacts on human health.

3.1.3 Health based approach for classifying chemicals of concern

Estimations of human health risks from exposure to specific chemicals are generally based on extrapolations of the results of toxicological experiments on animals. These extrapolations provide standard human 'dose-response' relationships for the chemicals. When considered along with estimations of human exposure to the chemicals, the risk from that exposure can be quantitatively estimated.

This approach has generally been used by health authorities for the determination of safe levels of specific chemical contaminants in drinking water. The approach is considered to be generally very effective for drinking water derived from relatively pristine sources or sources that have been used for a long time without any evidence of harm. However, current drinking water guidelines are not intended to ensure the safety of less traditional water sources such as recycled water. Furthermore, they should not be assumed to do so since wastewater may introduce novel, unidentified and/or unquantified sources of chemical contamination. Even if the operators of an IPR system could identify all of the chemical components in the processed wastewater, there would be scant toxicological data available for most of them and thus little basis for assigning risks. Because of this, and because many chemicals in wastewater are simply unidentifiable, it has been suggested that toxicological testing of recycled water may be the only way to ensure the

water's chemical safety (NRC 1998). Such testing will generally require at least a pilot-scale advanced water treatment plant to be constructed in order to provide relevant samples for testing.

Screening level risk assessments can be undertaken prior to the construction of any plant in order to assist in the identification of issues that may be relevant for more detailed risk assessment. A comprehensive example of a screening level health risk assessment was recently undertaken for Sydney Water's 'Replacement Flows Project' (Roser et al. 2006). The scheme was concerned primarily with the substitution of environmental flows with highly recycled treated water from three of Western Sydney's sewage treatment plants. The risk assessment did however estimate the health risks arising from the consumption of chemical (and microorganisms) loads likely to be emitted by the plant with and without further treatment as two of the possible exposure scenarios. The Screening Health Risk Assessment for this project was undertaken by initial consideration of historical monitoring data of chemical loads in the raw water source (tertiary treated effluent). Consideration of expected removal efficiencies of individual chemicals during advanced treatment processes and environmental residence allowed for estimations of human exposure. Comparison of this anticipated exposure with known dose-response relationships for individual chemicals provided an estimation of health risks associated with each one.

Chemical dose-response considerations form the foundation of most modern drinking water guidelines. However, direct chemical measurements are limited in that they will only identify the chemicals that are specifically targeted. This can only ever be a small subset of the all the chemicals that may possibly be present. Numerous decades of water quality monitoring have provided a reasonable (though always improving) understanding of which chemicals are likely to be present in drinking water from traditional sources at concentrations sufficient to present an elevated level of risk.

Other important limitations of chemical species monitoring are that the full additive toxicity of a large number of chemicals (mixtures), each present at very low concentrations, may not be identified unless each of the individual species is identified and determined to be present at concentrations greater than analytical detection limits. Finally, there is some concern that the toxicity of complex mixtures is poorly understood and in some cases may contribute to more (or less) toxicity than simply the additive impacts of each individual chemical species.

Toxicity testing of whole effluent mixtures may be undertaken by a variety of biological assays. Assays may generally be distinguished as *in vivo* or *in vitro*. These are Latin terms referring to whether the test is undertaken within a living organism (*in vivo*) or external to it such as testing of cells in a test-tube (*in vitro*). Some *in vivo* and *in vitro* tests that have been used for testing for the presence (or effects) of chemicals in complex water mixtures include the Ames test, sister chromatid exchange assays, the micronucleus test, the 6-thioguanine resistance assay, as well as testing for the induction of adenomas, toxic effects or bioaccumulation. This is further discussed in Section 4 of this document and in NRC (1998).

3.2 Chemical targets of concern

3.2.1 Introduction

Following the terminology of the National Guidelines for Water Recycling (NRMMC-EPHC 2006), each chemical agent that has the potential to cause harm to people, animals, crops or plants, other terrestrial biota, aquatic biota, soils or the general environment is a 'hazard'. A situation that can lead to the presence of, or exposure to, a hazard is termed a 'hazardous event'. 'Risk' is the likelihood of identified hazards causing harm in exposed populations or receiving environments in a specified timeframe, including the severity of the consequences. The national guidelines require that chemical hazards and hazardous events must be identified and evaluated.

Corresponding risks must be characterised and, when appropriate, preventative measures implemented to minimise the risks.

3.2.2 Source of different chemicals in found in sewage treatment plants

Chemical hazards consist of a wide range of naturally occurring and synthetic, organic and inorganic chemical species. They include industrial and household chemicals, chemicals excreted by humans and chemicals formed during wastewater and drinking water treatment processes, to name a few. The risks posed to human health by chemicals are also variable. Some chemicals may be acutely toxic, meaning that they impart toxic effects in a short period of time subsequent to a single significant dose. Others may be chronic health risks, meaning that long periods of exposure to small doses can have a cumulative detrimental effect on human health.

Central to the risk assessment concept is the necessity that each recycled water scheme or practice must be individually assessed based on the attributes of the specific system. It is therefore not appropriate to generalise about specific 'hazards', 'hazardous events' or 'risks' that exist for water recycling in Australia. However, it is a highly useful exercise to consider, in detail, the range of likely or potential 'hazards' which could be present in a typical recycled water scenario.

Phase 1 of the Australian Guidelines for Water Recycling (AGWR) provide a useful categorized list with some suitable representative chemical examples (Table 4.1 in NRMMC-EPHC 2006). The potential sources and overriding concerns of these categories and representative 'hazards' are reviewed in further detail below.

General characteristics		
• Biological oxygen demand (BOD) • Dissolved Oxygen (DO) • Hardness ($CaCO_3$) • Hydraulic load	• Odour • pH • Suspended Solids (SS) • Temperature	• Total dissolved salts (TDS) • Total organic carbon (TOC) • Turbidity

Source: All water parameters contribute to the general characteristics of the water, just from being present in the water body. These characteristics are traditionally indicators of water quality and have potential pollution implications. To a large degree, these parameters are those which are targeted for significant removal (or improvement) during conventional water and wastewater treatment operations. Thus in many cases, they are relied upon as indicators of the effectiveness of water treatment processes.

Nutrients		
• Boron • Calcium • Chloride • Iron	• Magnesium • Nitrogen • Phosphorus • Potassium	• Sodium • Sulphur

Source: The principal source of many nutrients in sewage is degraded organic matter derived from human excretions. Inorganic sources of nutrients include detergent formulations and in many cases, industrial wastewater influxes. Certain nutrients can be highly problematic since they sustain the growth of aquatic biota such as algae and cyanobacteria. In particular, nitrogen and phosphorus are typically 'limiting nutrients' in aquatic ecosystems, so an influx of these nutrients can very often lead to blooms of a wide variety of species. These phenomena can result in taste and odour problems, the production and release of toxic chemicals, and increased demand on dissolved oxygen leading to anaerobic conditions and the death of other aquatic species, including fish.

Metals/metalloids/halides		
• Aluminium	• Copper	• Mercury
• Arsenic	• Cyanide	• Molybdenum
• Barium	• Fluoride	• Nickel
• Beryllium	• Iodine/Iodide	• Selenium
• Bromate	• Iron	• Silver
• Cadmium	• Lead	• Tin
• Chromium	• Manganese	• Zinc

Source: Trace concentrations of many metals and halides in sewage will reflect those from the original drinking water supply. Additional contamination may result from industrial discharges dependant on the nature of industries within the catchment area. These are most commonly removed by partitioning to activated sludge in the sewage treatment process.

Surfactants		
• Alkane ethoxy sulphonates (AES)	• Linear alkylbenzene sulphonates (LAS)	• Secondary alkanesulphonates

Source: These chemicals are anionic surfactants used in commercial and domestic detergent products. Applications include dishwashing and clothes washing detergents as well as hair shampoos. Linear alkylbenzene sulphonates are the most common. Concerns regarding anionic surfactants are most likely because of their particularly high concentrations in raw sewages (1-20 mg/L). However, conventional wastewater treatment is effective at eliminating these chemicals from the aqueous phase, significantly reducing the associated risks of potential harm to environmental organisms.

Organic compounds		
• Acrylamide	• Dichlorobenzenes	• Polychlorinated biphenyls
• Alkyl phenols	• EDTA	• Phthalates
• Alkyltin compounds	• Epichlorohydrin	• Styrene
• Bisphenol A	• Hexachloro-butadiene	• Trichloro-benzenes
• Chlorinated dioxins	• Nitrilotriacetic acid	• Vinyl chloride monomer
• Chlorobenzene	• Polyaromatic hydrocarbons	

Source: The majority are synthetic industrial chemicals. Organic chemical compounds are highly variable in nature. The variability is a function of their origin (natural, anthropogenic), physical chemical properties, reactivity, susceptibility to biodegradation, ease of removal or persistence through advanced water treatment process and potential for human health impacts from benign to significant.

Volatile organics		
• Benzene	• Ethylbenzene	• Trichloroethene
• Carbon tetrachloride	• Tetrachloroethene	• Xylenes
• Dichloroethanes	• Toluene	
• Dichloromethane	• 111-trichloroethane	

Source: Volatile organic compounds (VOCs) are widely used as industrial solvents. The non-halogenated compounds are constituents of many petrochemical products, while the most of the halogenated compounds may be formed as byproducts of chlorine disinfection.

Pesticides or their metabolites		
• 2,4-D	• Chlorpyrifos	• Heptachlor and epoxide
• Aldicarb	• DDT	• Lindane
• Aldrin/Dieldrin	• Diuron	• Organic mercurials
• Atrazine	• Diazinon	• Organo-phosphates
• Carbamates	• Endosulfan	• Pyrethroids
• Chlordane	• Fungicides	

Source: Pesticides may enter municipal wastewater systems by a variety of means including stormwater influx and illegal direct disposal to sewage systems. Additional routes, of unknown significance, include washed fruit and vegetables prior to household consumption; insect repellents washed from human skin; flea-rinse shampoos for pets; and clothes and equipment used for applying pesticides.

Algal toxins		
• Cylindro-spermospin	• Nodularin	• Saxitoxins
• Microcyctins		

Source: Microcyctins, nodularins, cylindrospermopsin and saxitoxins are all produced by freshwater cyanobacteria. Under suitable conditions, cyanobacteria may grow in recycled water, producing these and other toxins. Cyanobacterial growth and toxin production may also occur subsequent to water treatment processes in environments such as storage tanks or ponds.

Disinfection byproducts		
• Chloral hydrate	• Chlorite	• Haloacetonitriles
• Chlorate	• Chlorophenols	• Haloaldehydes
• Chloride	• Chloropicrin	• Haloketones
• Chlorine dioxide	• Cyanogen	• Trihalomethanes
• Monochloramine	• Formaldehyde	
• Halogenated furonones	• Haloacetic acids	

Source: Disinfection byproducts are formed by reactions between disinfection agents and other constituents of water such as high concentrations of organic components or ammonia. The vast majority of these compounds originate primarily from chlorine-based disinfectants. Some more recent byproducts of concern (not listed here) include bromate (from ozone treatment) and nitrosodimethylamine (NDMA).

Radionuclides		
• Radium -226 and 228	• Radon -222	• Uranium generated (Cs137, Sr90 etc)

Source: Radionuclides may enter sewage by natural run-off or as a result of medical or industrial use. In most parts of the world, radium is a constituent of bedrock and hence a natural constituent of groundwater. Radon is a carcinogenic gas which comes from the radioactive breakdown of radium. Uranium-generated radionuclides (including Cs137 and Sr90) are produced during uranium fission reactions.

Pharmaceuticals

- Oral contraceptives
  - Levonorgestrel
  - Ethinylestradiol
- Analgesics
  - Ibuprofen
  - Paracetamol
  - Morphine
  - Naproxen
  - Ketoprofen
- Other pharmaceuticals
  - Methamphetamine
  - Phenytoin
  - Carbamazepine
- Radiopharmaceuticals
- Sedatives
  - Temazepam
- Cardiovascular drugs
  - Beta blockers
  - Atenolol
- Cholesterol lowering
  - Simvastatin
  - Gemfibrozil
- H. receptor agonists
  - Ranitidine
- Antibiotics
  - Cephalexin
  - Cefaclor
  - Amoxicillin
  - Metronidazole

Source: Pharmaceuticals (and their metabolites) may be discharged to sewage via human excretions as well as direct disposal of unused drugs by households. Industrial discharge is a relatively minor contributor due to the tight regulation of pharmaceutical industries.

Estrogenic and androgenic hormones

- 17β-estradiol
- Estrone
- Testosterone

Source: The estrogenic and androgenic hormones listed here are natural steroids excreted by humans. For example, in the normal menstrual cycle 10-100 µg/day of 17β-estradiol is typically excreted by women depending on the stage of the cycle. During pregnancy, up to 30 mg/day may be excreted. After menopause, estrogen excretion typically drops to around 5-10 µg/day. Men also excrete estrogens at a rate of about 2-25 µg/day (Williams & Stancel, 1996). During metabolism, estradiol is primarily converted to estrone and further to estriol, which is the major urinary metabolite. Testosterone, secreted by the testis is the main androgen in men, along with its similarly active metabolite dihydrotestosterone. These natural androgens are metabolised and excreted in urine as both free steroids and water-soluble conjugates. This group of chemicals is discussed in more detail in Section 5.

Antiseptics

- Triclosan
- Salicylic acid

Source: Antiseptics such as triclosan are commonly used in face washes and anti-gum-disease toothpaste. Following trends from the USA, they are increasingly being used in a wider range of household products including deodorants, antiperspirants, detergents, dishwashing liquids, cosmetics and anti-microbial creams, lotions, and hand soaps.

3.3 Preventative Measures: Source Control as a barrier for chemicals

Source control is a regulatory management practice to minimise the discharge of pollutants into the sewer. Best management practices of source control or source protection ensure sustainability and integrated pollution control of the wastewater. Control at the source reduces the treatment costs and improve the reliability of water quality. Effective source control practices involve the following elements

1. Developing and executing catchment management plan
2. Ensuring that the planning regulations are made to protect water resources from potentially polluting activities
3. Trade waste monitoring and compliance assesment
4. Creating awareness within the community towards the impact of anthropogenic activities on water quality

3.3.1 Catchment management

Catchment management is a planning approach to maintain sustainable resource management, understanding the role of the ecosystems and the processes involved with the habitats. Catchment management helps in implementing policies and strategies to minimise the contaminants entering the water, benefiting both the ecosystem and the stakeholder. Catchment planning aims to protect water resources from polluting activities, thus maintaining water quality. It also takes necessary action on the priority threats.

3.3.2 Planning and zoning within the catchment

The preparation, amendment and adoption of the comprehensive plan for the catchment management will better help maintaining the water quality management. Some of the action plans within the catchment include,

- Delineating the boundaries included for the source control
- Identifying the environmental limits of the various parts of the environment
- Registering the various chemicals used in the catchment (inventory)
- Specific protective requirements for certain chemical industries or allied stations
- Reservoir mixing, pH adjustment of the reservoir water
- Closely communicating with the local catchment community
- Self monitoring and auditing the whole process at various levels.

3.3.3 Features of the trade waste monitoring and enforcement programme

Trade waste is water borne waste discharged from a trade premises during a trade or industrial operation, process or manufacture. Trade waster does not include domestic wastewater or stormwater. Trade waste has the potential of containing a large range of harmful chemicals, such as heavy metals, organic solvents, oils and greases, chlorinated organic compounds, and pesticides.

Sewerage systems are generally designed to safely collect wastewater from domestic origin for treatment at the sewage treatment plant. Discharged liquid trade waste adds an additional load on the sewerage system and sewage treatment plant and may result in:

- the release of odours and offensive gases
- hastened corrosion of sewer infrastructure
- altered sewage treatment processes
- increased public health and safety risks
- affected community assets

Nevertheless, the sewage systems have usually been designed, and are therefore capable of treating liquid trade waste, provided that the discharges are well defined and within acceptable limits. In certain cases, trade wastes are difficult to treat separately and are more effectively removed when mixed, and treated, with domestic sewage. In trade waste treatment systems / reuse systems, trade waste policies will be implemented to control these recalcitrant chemicals. Trade waste policies usually have regulative restrictions and requirements and pricing controls that limits the quantity and nature of discharged trade wastes.

Trade waste generators are responsible for being aware of the wastewater utility's requirements and policies. Also the waste generators should get appropriate approval from the respective board before discharge. It is also the responsibility of the trade waste generators to make certain that chemicals used in their primary treatment process does not affect the downstream wastewater treatment system.

It is the responsibility of the local water utilities to implement best management practices in controlling and pricing liquid trade waste. The responsibilities of a wastewater utility / treatment entity are that they should monitor and ensure that the trade waste;

- does not create any adverse impact on the sewage or affects the environment
- does not cause any odour complaints or create any hazards to public health and safety
- does not create health and safety issues for workers
- does not create any system overflow or affect the management of effluent quality
- has been measured and monitored for its quality and quantity
- pricing has been fixed for the trade waste dischargers

The successful implementation of trade waste management (including pricing) and best practices will result in improved sewerage performance, improved environmental outcomes and reduced costs.

Trade waste policy is also a key component of, and highly relevant to, indirect potable recycling schemes. The following sections describe the trade waste approach in Australia. An example from Orange County of how trade waste controls and policy can compliment indirect potable recycling projects, by the removal of chemicals that persist through advanced water treatment systems, will be presented.

3.3.4 Assessment of comparable source control monitoring and enforcement and catchment planning in Australia

Australian water utilities have a well established practice of regulating chemicals discharged to sewer, as part of their overall pollution abatement processes. The minimisation of waste discharge at the source has been practiced by many Australian industries and organisations. Trade waste programs are being demonstrated as being an effective application to achieving natural resource sustainability. The following section provides an overview of source control (trade waste) mechanisms for three major water authorities.

Gold Coast Water (GCW), Queensland: This entity is responsible for water supply and wastewater services to all domestic, commercial and industrial premises in the Gold Coast city council region. GCW is responsible for the water resources and maintaining the sewage treatment system. GCW administers a trade waste policy to monitor and regulate the quality of trade waste using an electronic monitoring and management system, 'water safe', for tracking liquid waste. It monitors the removal and disposal of waste from grease traps and other pretreatment devices and holding tanks. GCW developed a risk-based formula for determining the customer's category, and defining the impact of each trade waste producer on the sewage treatment system. Each trade waste customer is monitored through various methods such as a property water meter, process water meter and electronic equipment measuring trade waste discharge, and charged directly or indirectly. GCW may terminate a trade waste approval if the respective holder (business / activity) does not comply with;

- Terms and conditions of the approval
- Provisions of the Water Act 2000
- Council's waste management plan
- Requirements of any written notice issued by GCW
- When immediate actions need to be taken in the interest of public health and safety

Implementation of this trade waste management system assists GCW to protect the environment and waterways, limits damage to Gold Coast's wastewater system and protects public health. (http://www.goldcoast.qld.gov.au/t_gcw.asp?pid=4123)

Sydney Water, NSW: Sydney Water provides drinking water, recycled water and wastewater services to Sydney, Illawara and the Blue Mountains. To maintain ecological sustainability, the trade waste policy was written in 1988, and updated by a trade waste policy and management plan in 1991. It has been administered by the wastewater source control branch through negotiated agreements with industry. The policy consists of direct regulation and user charges, aimed at controlling trade wastes from being discharged into the system. The trade waste policy is supported by two management plans (for commercial and industrial customers) and number of fact sheets. The discharge of intractable wastes, and other prescribed hazardous substances, is strictly banned. Trade waste charges are imposed on the user pays basis, according to the nature of substance, effluent concentration and total load.

Sydney Water's trade waste program is aimed at managing wastewater at the source. It focuses on the possible measures that can be employed to minimise the concentration of pollutants in the wastewater before they enter the treatment system. It greatly encourages industrial and commercial customers to adopt best available technologies and cleaner production methods to regulate their discharges to the Sydney Water's wastewater treatment system. The hierarchy of the available options available are;

1. Green chemistry
2. Cleaner production technology
3. Pre-treatment
4. Dilution.

Trade waste policy has been successful in ensuring Sydney Water's wastewater operations meet environmental regulations, thus helping to protect the environment and public health. Monitoring results have shown that the discharge of pollutants have declined since the plan was introduced. The improvement in the environmental quality of the receiving waters has been observed and this improvement is expected to continue.
(http://www.sydneywater.com.au/OurSystemsAndOperations/Tradewaste/)

***City West Water, Victoria*:** In Australia, water agencies like City West Water (CWW) have taken an approach called Integrated Sewage Quality Management System (ISQMS) based on methods used in the food industry that relate to supply chain management as certified by ISO 22000. The approach at CWW is based on the following five risk management drivers,

1. People – the health of sewer workers
2. Pipes – sewerage system infrastructure
3. Processes – wastewater treatment plant processes
4. Environment – treatment plant discharges, odour
5. Recycling – opportunities to recycle water and biosolids

This approach is based on a bulk wastewater agreement where the wastewater quality management system (SQMS) is the risk driver, aiming at dealing with treatable pollutants (BOD, SS, TKN to be treated for Melbourne Water), other pollutants including critical pollutants, and acute event risks such as pesticide spills. An internal audit is undertaken at regular intervals to identify any problems and acts as a focal point for continual improvement. The SQMS is audited every two years and reviewed every three years.

The proposed management approach, ISQMS, has been modified, according to water and wastewater industry requirements, to be consistent with the Australian Drinking Water Guidelines, Australian Guidelines for Water Recycling, EPA VIC dual pipeline guideline and WSAA source control guidelines. It assures product safety from the beginning of the chain through to the consumer using four key elements; interactive communication, system management, prerequisite programs and HACCP principles. Elements on any ISO 22000 system include;

1. Scope
2. Management system
3. Management responsibility
4. Resource management
5. End product characteristics
6. Process description
7. Hazard analysis
8. General prerequisite programs
9. Operational prerequisite programs
10. HACCP plan (engineers risk treatment)
11. Emergency preparedness and response
12. Verification schedule
13. Validation schedule
14. Review and improvement plan

The ISQMS plan will be structured, documented and carried out in line with these ISO 22000 elements, and allows for external certification. Three key risk categories considered in the application of the ISQMS plan include treatable pollutants (e.g., BOD), incremental risks (e.g. salinity) and acute event risks (e.g. pesticide spills).

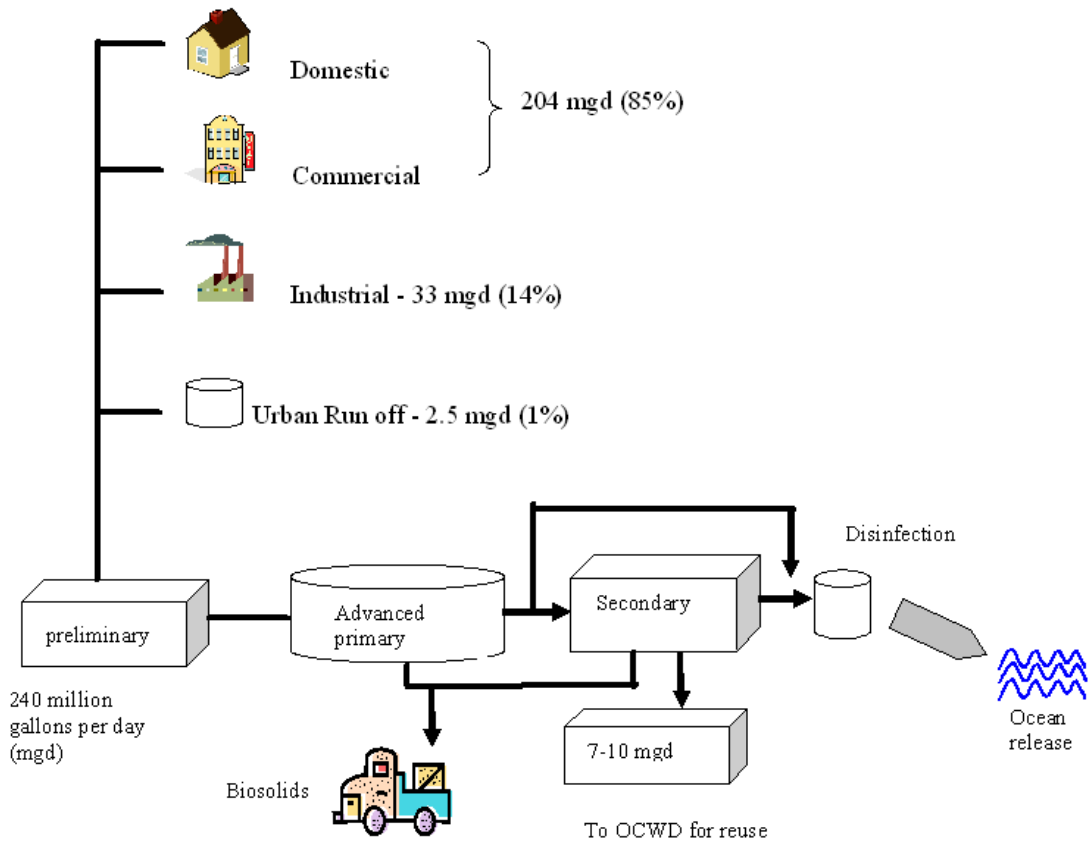
A benefit of ISO 22000 certification process will be a source control system that is based on 'end use' quality and preventative risk management techniques which is consistent with the framework for the Australian Drinking Water Guidelines (ADWG) and the National Water Guidelines for Water Recycling (NGWR) (City West Water, 2007).

3.3.5 Case study - Orange County Sanitation District (OCSD)

Orange County Sanitation District (OCSD) took a proactive stance on enhanced source control for chemicals of concern in drinking water. This greatly supports the large scale water recycling through Ground Water Replenishment (GWR) system. OCSD has authority to regulate the discharges to sewer that affect the water recyclability. Also OCSD is committed to reinvent source control for the quality assurance of GWR system. The major goals of the Enhanced Source control program include;

- developing an inventory of chemicals and analytical methods to test the wastewater for contaminants
- investigating the sources of pollutants and understanding the pollutants of concern
- expanding industrial sampling and monitoring of pollutants
- increasing the industrial educational outreach plan and creating a regional approach

Figure 3-2: Orange County Sanitation District – Process flow diagram



OCSD receives 240 MGD / day of wastewater; 85% is domestic and commercial wastewater, 14% is industrial wastewater and 1% is urban run off. The influent is treated in preliminary, advanced primary and secondary treatment processes. 86 MGD of secondary treated effluent is taken for further treatment through membrane processes (ultrafiltration and reverse osmosis) and disinfection. 7 -10 MGD / day of purified recycled water is then sent for natural soil filtration.

OCSD's initial source control efforts is aimed at reducing the concentration spikes of N-Nitrosodimethylamine (NDMA) and 1, 4-Dioxane thus supporting the water recycling efforts of the Orange County Water District (OCWD). The removal of these chemicals is a difficult process. NDMA has been identified as "reasonably anticipated to be a human carcinogen" (US EPA, 1997). Also NDMA has been identified as a carcinogen under California's Health and Safety code Section 25249.5, *et.seq.*, and the Safe Drinking Water and Toxic Environment Act of 1986 ("proposition 65"). In 2000, NDMA concentrations in the RO permeate were found to be above the action level of 20 parts per trillion (ppt), ranging from 100 to 1500 ppt in the sewer. The estimated concentration of an additional lifetime cancer risk of 1 in 1 x 10^6 through the consumption of drinking water is 1.4 ppt. It has been identified that the use of Dimethyldithiocarbamate (DTC) is a major precursor for NDMA. DTC is a chelating agent used in industries for removal of metals from their wastewater and is therefore found in water and wastewater treatment plants.

The occurrence of NDMA in different parts (trunks) of the sewerage system varies depending on the time of the day (Table 3-1). The residential trunks (Newhope and Euclid) had the lowest NDMA concentration of 30 and 33 ppt average daily concentration respectively.The industrial trunk (Airbase) had the highest concentration of 1002 ppt. The other two trunks (Sunflower and Talbert), which were mixed sewage, had NDMA concentrations of 480 and 472 as average daily

concentration respectively. The sampling was performed every four hours, and it was observed that the peak NDMA concentration spike observed between 12.00 p.m and 8.00 p.m.

Table 3-1: Diurnal variation NDMA concentration (as ppt)[1] in sewer trunks tributary to plant No. 1

Time	Trunk Name				
	Airbase	**Euclid**	**Sunflower**	**Talbert**	**Newhope**
8.00 a.m.	1350	<20	580	510	<20
10.00 a.m.	NA	NA	NA	NA	NA
12.00 p.m.	780	37	450	950	na
2.00 p.m.	NA	NA	NA	NA	24
4.00 p.m.	1060	23	440	250	25
6.00 p.m.	NA	NA	NA	NA	NA
8.00 p.m	920	<20	440	440	<20
10.00 p.m.	NA	NA	NA	NA	NA
12.00 a.m	1520	<20	550	410	<20
2.00 a.m.	NA	NA	NA	NA	NA
4.00 a.m.	380	<20	420	270	50
6.00 a.m.	NA	NA	NA	NA	NA
Average Daily Conc.	**1002**	**30**	**480**	**472**	**33**

1. Based on a detection limit of 20 ppt
na = not available; extract was not reinjected

1,4-dioxane can be present in wastewater from industrial sources since it is commonly used as a solvent in various sectors such as metal finishing, fabric cleaning, electronic, pharmaceutical, herbicides and pesticides production, and antifreeze and paper manufacturing. The United States EPA has classified 1,4-dioxane as a Group B2, probable human carcinogen. In 2001, the amount of 1,4-Dioxane was found to be above the action level of 3 ppb in the RO permeate.

The source control measures for NDMA and 1, 4-Dioxane started with investigation of pollutant concentration levels in various trunk lines including domestic and industrial discharge points. The lines with larger contaminant load were suitably diverted for appropriate pollutant level management. With industry co-operation, the use of NDMA precursors and 1,4-dioxane was reduced. Partial nitrification and denitrification, to reduce total nitrogen (specifically ammonia and nitrate, precursors to NDMA), were also performed.

After the application of multiple barriers, source control, biological nutrient removal, reverse osmosis and UV irradiation, the NDMA concentrations decreased significantly. The amount of 1,4-dioxane fell back below the action level. A summary of NDMA removal efficiency for various multiple barriers is presented in Table 3-2.

Table 3-2: Summary of NDMA removal efficiency for proposed multiple barriers

Barrier	NDMA Concentration (ppt)		Removal Efficiency
	Influent	**Effluent**	
One: Source control/BNR	348[1]	200	40%
Two: Demineralisation[2]	200	100	50%
Three: Advanced oxidation[3]	100	10	90%

1 - Influent concentration expressed as 90th percentile
2 - Demineralisation via RO will be addressed in section 5.
3 – NDMA removal through advanced oxidation technique will be addressed in section 5.

3.4 Process Barriers: Removal efficiency of advanced water treatment processes

3.4.1 Mechanism for chemical removal based on separation, adsorption or oxidation

Advanced water recycling technologies have both advantages and limitations when involved in the treatment and removal of chemical contaminants. The selection and compilation of the assorted available treatment options will depend on a diverse range of economic, environmental and social constraints and requirements.

Advanced biological treatment most commonly relies on the expanded employment of micro-organisms for the degradation and/or assimilation of chemical contaminants. Most notably, the use of anaerobic and anoxic conditions for processes such as denitrification have greatly expanded the range treatable contaminants compared to traditional aerobic processes. An approach particularly suited to many advanced water treatment schemes is known as 'biological activated carbon' filtration. This process involves the percolation of water through a granular activated carbon system on which a heavy biofilm has been established. While the activated carbon retains contaminants by adsorption, micro-organisms in the biofilm enhance the process with biodegradation.

Chemical treatment of waterborne chemical contaminants is typically undertaken with oxidants such as hydrogen peroxide and ozone. These processes may result in the direct molecular degradation of the target molecules, and/or produce by-products that are more amenable to a secondary physical or biological removal step. Chemical treatment processes can be highly effective, however in some cases they can also be expensive to install and operate. Since they degrade, rather than remove, contaminants, further issues arise with degradation products and byproducts which may, in some instances, be of greater concern than the initial contaminants.

Photochemical degradation of chemical contaminants may be induced by exposure to natural sunlight or facilitated by an ultraviolet radiation (UV) source. When waters are exposed to UV radiation, reactive species such as hydroxyl and oxygen radicals may be produced. These in turn react to disinfect, as well as to degrade trace chemical species (Rosenfeldt & Linden, 2004). Photochemical treatment relies on low turbidity, which recycled water often does not conform. UV degradation of chemical contaminants is still an emerging technology, and likely that very high dosages are required for the removal of some of the more recalcitrant chemical species.

Physical methods of removing chemical contaminants have traditionally relied on adsorption of target contaminants onto either fixed solid surfaces (as in sand or granular activated carbon filtration) or suspended particulates such as iron or aluminium oxyhydroxides, or powdered activated carbon. Further advanced physical treatment processes rely more on size-exclusion than simply on adsorption processes, and hence these processes may present a more reliable barrier. Membrane filtration processes such as microfiltration, nanofiltration, ultrafiltration and reverse osmosis may result in significantly improved treatment of some key chemical compounds. The low porosity membrane operations (particularly reverse osmosis) have rapidly become the most universally accepted means of the assured removal for most chemicals.

3.4.1.1 Semi-permeable membranes for reverse osmosis processes

Reverse osmosis (RO) is a broad-spectrum treatment process capable of continuously removing ionic and non-ionic species. The process is driven by a pressure gradient that forces molecules across a semi-permeable membrane. These RO elements are produced by several manufactures in various sizes to fit all commercially available RO pressure vessels. The uniform design of the RO element and pressure vessel has promoted competition between RO manufactures resulting in

technical innovations that have reduced RO operating pressures, increased salt and chemicals rejection, and decreased manufacturing costs.

Reverse osmosis membranes are configured as flat sheets. The sheets are folded over a porous spacer and sealed on three sides to create and envelope. The open side is sealed onto a perforated tube that will carry permeate that passes across the membrane and travels through the porous spacer. The active surface which is located on the outside of the envelope is wrapped in a mesh spacer. The mesh encased membrane is wound around the central permeate tube to create a spiral wound element with channels defined by the mesh spacer (Figure 3-3). Individual elements are coupled together along the permeate tube and loaded into a pressure vessel (Figure 3-4). A bank of pressure vessels is connected to a high pressure feed manifold located on the discharge side of the high pressure feed pump (

Figure 3-5). Water under pressure is forced through the channels in each element defined by the mesh spacer. A portion of the feed water travels across the membrane and collects in the permeate tube while the balance of the water is discharged as concentrate out the end of the vessel. The ratio of permeate produced to the feed water is refered to as the process recovery. The feed pressure required is determined by the pressure loss through the channels plus the sum of the pressure loss across the membrane and the osmotic pressure of the salts retained on the membrane surface. Typical feed pressures in wastewater reclamation applications range from 8 to 14 bar with the system operating at 75-85% recovery. In contrast, feed pressures for desalination systems range from 60 to 80 bar with the system operating at 35 to 45% recovery. The difference in operating conditions in desalination compared with wastewater reclamation may be attributed to the higher concentration of salt in the feed water which in turn increases the osmotic pressure on the membrane surface.

The first RO membranes were developed in the 1950s for seawater desalination applications. The membranes were relatively rigid and thus self-supporting. They were produced by precipitation of soluble cellulose acetate polymer in a non-solvent (referred to as a liquid-solid phase inversion process). By the mid 1970s, the membranes were made by a polycondensation process whereby polyamide is deposited as a thin film on a porous substrate. Cellulose acetate membranes were first used in AWT plants in 1976 at California's Water Factory 21. However, by the late 1990s thin film composite (TFC) membranes had become the industry standard for both seawater desalination, wastewater recycling and industrial water treatment.

Figure 3-3: Schematic of a single reverse osmosis element.

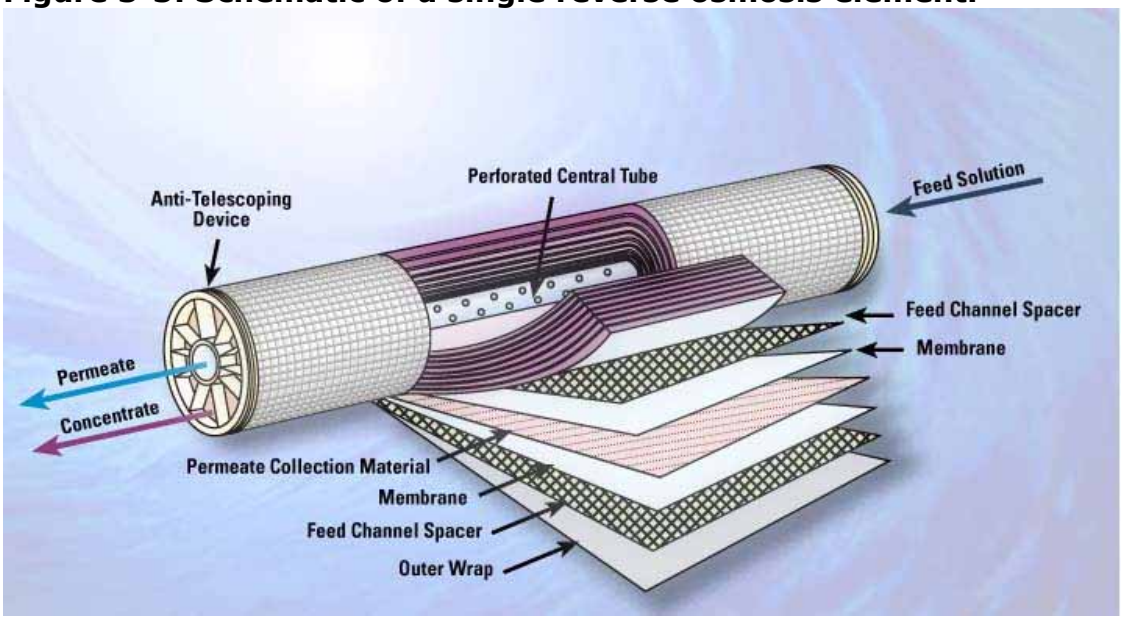


Figure 3-4: Assembly of multiple reverse osmosis membrane elements into a pressure vessel.

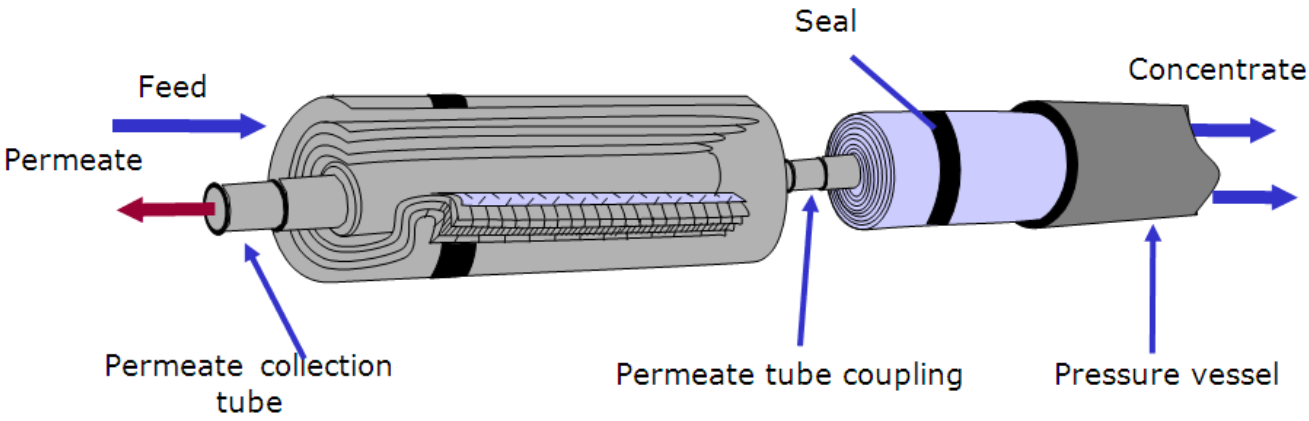


Figure 3-5: Arrangement of pressure vessels into a single system.

Thin film composite membranes have been designed with chemical functional groups attached to the membrane surface to facilitate electrostatic repulsion of susceptible chemicals in the feed water. Such functional groups include sulfonic acid and carboxylic acid groups, which are negatively charged under normal pH conditions (typically pH 6-8). Solutes which are also negatively charged (including many pharmaceuticals and EDCs) can be efficiently rejected by such membranes (Ozaki & Li, 2002).

3.4.1.2 Adsorptive treatment processes

IPR schemes that operate in jurisdictions where it is not necessary to meet a final water quality target for total dissolved solids (TDS) tend to employ adsorptive treatment processes to remove chemical molecules. Examples include Loudoun County (Virginia) and Gwinnett County (Georgia) in the USA.

Among the most well-established processes for advanced trace chemical removal is adsorption to activated carbon. This is a form of carbon usually derived from charcoal. The term 'activated' refers to the way the carbon has been prepared to enhance its ability to physically 'adsorb' chemicals to its surface. Adsorption is the accumulation of a dissolved chemical (solute) onto a solid surface.

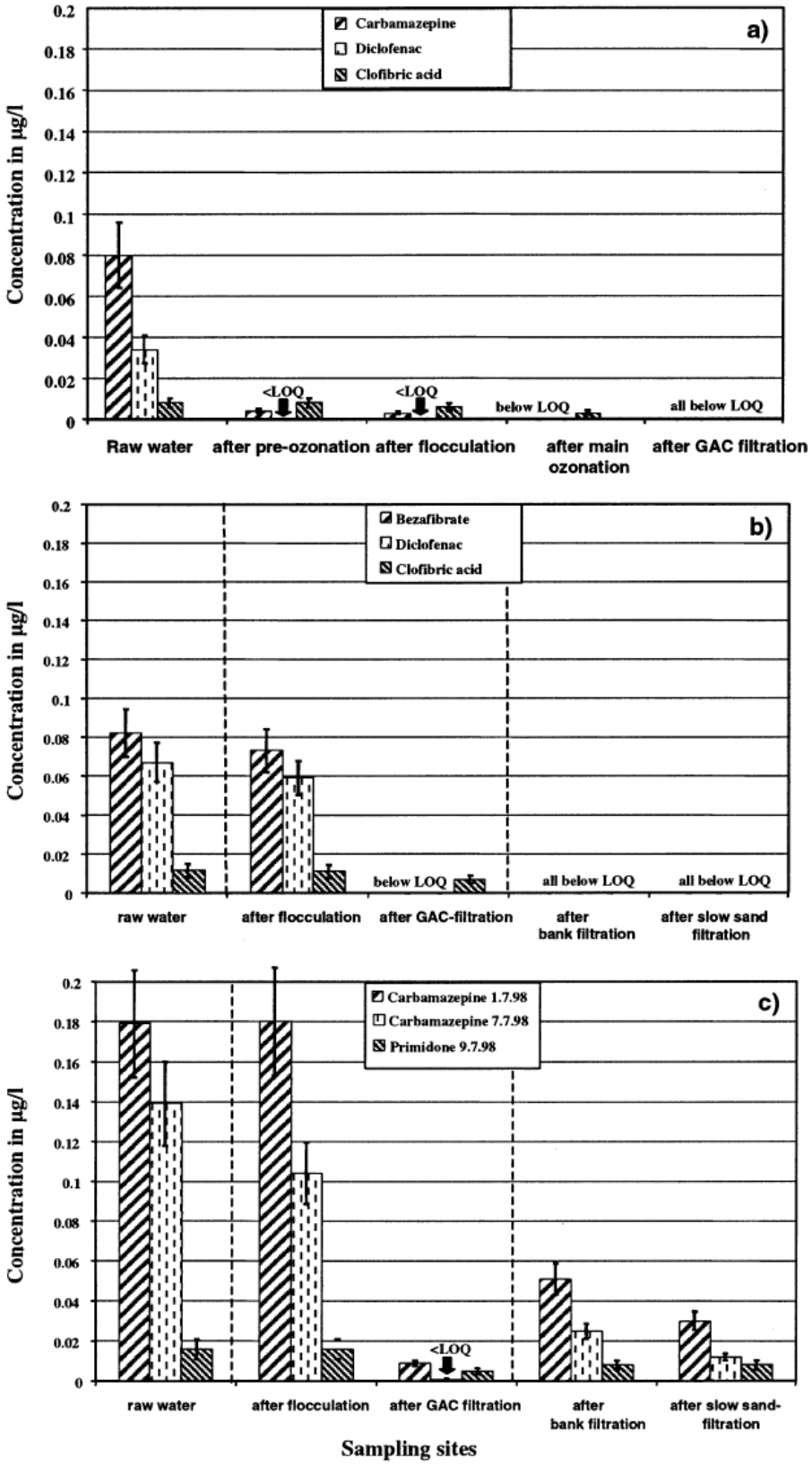
An important property of activated carbon is its extremely high surface area. One gram (about a teaspoon full) of activated carbon can have a surface area of 400-2000 square metres. By comparison, a tennis court is about 260 square metres. A microscopic view of activated carbon reveals a complex web structure intermingled with trapped smaller particles. There are many nooks and crannies, which provide excellent conditions for adsorption of suitable chemicals.

The most common applications of activated carbon for water treatment are known as granular activated carbon (GAC) and powdered activated carbon (PAC). These terms refer to the physical form (particle size) in which the activated carbon is applied. Smaller particle sizes in PAC tend to have higher surface areas while large particle sizes (GAC) tend to be more easily separated from the water subsequent to treatment. PAC is often used by direct addition to water with mixing and then separated by gravity and/or filtration. Alternatively, GAC is more commonly used as filtration media with the water being percolated through it.

The effectiveness of PAC and GAC to adsorb a particular chemical can generally be predicted based on how 'hydrophilic' or 'hydrophobic' the chemical is. These terms refer to the tendency of a chemical to partition preferentially into aqueous phases (hydrophilic) or non-aqueous phases (hydrophobic). PAC and GAC are effective for the removal of a diverse range of hydrophobic organic compounds as well as well as some relatively hydrophobic inorganic compounds such as nitrogen, sulphides and heavy metals. More hydrophilic compounds, such as small carboxylic acids and alcohols, are relatively poorly removed by activated carbon adsorption (Metcalf & Eddy Inc. 2003).

The parameter most commonly used to describe how well a chemical can be adsorbed to activated carbon is known as the Freundlich capacity factor (Dobbs & Cohen, 1980).

Figure 3-6: Concentrations of pharmaceuticals during drinking water treatment including GAC (Ternes *et al.*, 2002)



The Freundlich capacity factor is determined experimentally by testing various ratios of chemical concentration and activated carbon surface area in otherwise pure water under controlled conditions. A high Freundlich capacity factor indicates that the chemical is very effectively adsorbed, while a low Freundlich capacity factor indicates that the chemical is poorly adsorbed.

The range of Freundlich capacity factors for potential water contaminants is extremely wide. For example, polychlorinated biphenyls have Freundlich capacity factors greater than 104 while NDMA has a Freundlich capacity factor of around 10^{-4}. Because of this wide variation, the Freundlich capacity factor must be determined for each specific compound (Metcalf & Eddy. Inc., 2003). As a further complication, specific mixtures of compounds in a raw water source will affect the adsorptive capacity for each chemical.

PAC has been shown to be highly effective for the removal of a wide range of pharmaceuticals, endocrine disruptors and pesticides from relatively clean water sources (Adams et al., 2002; Westerhoff et al., 2005). A study recently undertaken at the Southern Nevada Water Authority provides a useful illustrative example (Westerhoff et al., 2005). For this research, raw drinking water supplies were collected and high concentrations of 62 different chemicals were spiked into them. These waters were then treated by a number of laboratory-scale water treatment processes including PAC. Addition of 5 mg/l of PAC with a 4 hour contact time removed different compounds by between 10% to greater than 98%. Higher PAC dosages improved the removal of most chemicals. This study confirmed that the removal effectiveness for specific chemicals could be reasonably well predicted based on their lipophilicity.

GAC has also been shown to be effective for the removal for some important chemical contaminants in water. For example, Ternes et al. (2002) investigated the removal of some pharmaceuticals during a range of drinking water treatment processes. The particular pharmaceuticals were some that are commonly reported in European drinking water sources including carbamazepine, diclofenac, clofibric acid, bezafibrate and primidone. This study revealed GAC filtration to be an effective method for removing most of the studied compounds. Figure 3-6 shows the relative concentrations of some of these chemicals that were actually measured in raw drinking water sources (that is, they were not artificially spiked in). The dotted lines in Figure 3-6 indicate parallel treatment processes. It can be seen that GAC treatment, in combination with other conventional treatment processes, significantly removed most of the pharmaceuticals. In a number of cases, remaining concentrations were reported to be below the limit of quantitation (LOQ). This simply means that the concentrations were too low to be reliably measured.

These studies are consistent with the conventional understanding and application of activated carbon treatment processes. Used as a component of a carefully selected suite of treatment processes, activated carbon has an important role to play in water purification.

3.4.1.3 Advanced oxidation processes

Oxidative processes may used to degrade any chemical constituents of wastewaters that prove to be both biologically recalcitrant and poorly retained by membranes or activated carbon. Strong chemical oxidants such as ozone (von Gunten, 2003), potassium permanganate (Adam *et al.*, 2004; Chen *et al.*, 2005) and chlorine (Chamberlain & Adams, 2006; Choi *et al.*, 2006) have been shown to be effective for the degradation of chemical contaminants in water.

Oxidative degradation can occur either by direct reaction with the applied oxidant, or via the production of highly reactive secondary species, most commonly, hydroxyl radicals (●OH). The hydroxyl radical is one of the most powerful oxidants known.

Ultraviolet (UV) radiation can also be used to degrade organic chemicals in water (Rosenfeldt *et al.*, 2005; Shemer *et al.*, 2005). Furthermore, UV radiation is also commonly used to promote the formation of hydroxyl radicals. This can be achieved by a number of methods including

photocatalysis with titanium dioxide (TiO_2) (Egerton *et al.*, 2006; Murray & Parsons, 2006) or by direct reaction of hydrogen peroxide (H_2O_2) (Rosenfeldt & Linden, 2004; Shemer *et al.*, 2006a; Shemer & Linden, 2006; Shemer *et al.*, 2006b).

Processes which promote the enhanced formation of hydroxyl radicals are generally referred to as advanced oxidation processes (AOPs). Most commonly, AOPs for water treatment are achieved by the addition of hydrogen peroxide to ozone or UV contact chambers. An alternative approach, known as Fenton's processes use ferrous ions to catalyse hydrogen peroxide degradation under acidic conditions (Shemer *et al.*, 2006a). The key chemical reactions for the production of hydroxyl radicals using hydrogen peroxide are:

Ozone/H_2O_2: $H_2O_2 + 2\ O_3 \rightarrow 2\ \bullet OH + 3\ O_2$

UV/H_2O_2: H_2O_2 + UV (wavelength 200-280 nanometres) $\rightarrow 2\ \bullet OH$

Fe^{2+}/H_2O_2: $H_2O_2 + Fe^{2+} \rightarrow \bullet OH + OH^-$

For optimum efficiency of advanced oxidation processes, an optimal concentration of H_2O_2 exists (Wu *et al.*, 2007). At excessively high concentrations, the reaction between H_2O_2 and hydroxyl radicals produces $HO_2\bullet$, which are much less reactive compared to $\bullet OH$ radicals, thus H_2O_2 effectively acts as a radical scavenger. Furthermore, at higher concentrations, H_2O_2 may effectively absorb UV light, thus reducing the effectiveness of any important direct photolysis reactions.

Both ozone (von Gunten, 2003) and UV radiation (Rosenfeldt & Linden, 2004) by themselves can be used to degrade chemical contaminants to some degree. However, without the enhanced generation of hydroxyl radicals, molecular ozone or UV radiation alone are relatively specific in the chemical groups that they attack. Conversely, oxidation of organic chemicals by hydroxyl radicals is non-specific and all organics are ultimately susceptible if sufficient dose is applied (Lopez *et al.*, 2003; Shemer *et al.*, 2006b).

Quantum yield (Φ) and molar absorption are two fundamental parameters that govern the rate of direct photodegradation. The quantum yield is defined as the number of moles of photochemical product per moles of photons absorbed. The overall photolysis rate of a particular chemical and the quantum yield are calculated by the following equations:

$$-\frac{d[chemical]}{dt} = k\ d[chemical] = k_{s,\,chemical}\,\Phi_{chemical}$$

$$\Phi_{chemical} = \frac{k_d}{k_{S,chemical}}$$

Where:
$\Phi_{chemical}$ is the quantum yield of the particular chemical
k_d is the pseudo first-order rate constant
$k_{S,chemical}$ is the specific rate of light absorption by the chemical ($E.mol^{-1}.s^{-1}$)

Many chemical contaminants will be variably susceptible to direct photolyisis and indirect photoylsis via hydroxyl radicals during advanced oxidation processes. An overall kinetic rate model for degradation can thus be described as (Pereira *et al.*, 2007):

$$Rate = -\frac{d[C]}{dt} = (k_d^{'} + k_i^{'})[C]$$

Where:

K'_d = direct photolysis rate constant
K'_i = indirect photolysis rate constant
The direct photolysis rate constant can be modelled by the following:

$$k'_d = \Phi(\sum k_s(\lambda))$$

Specific rate of light absorbance (Es.mol^{-1}.s^{-1}) $k_s(\lambda) = \frac{E_p^o(\lambda)\varepsilon(\lambda)[1-10^{-a(\lambda)z}]\times 1000}{a(\lambda)z}$

Φ = photolysis quantum yield (mol Es^{-1})
E_p^0 = incident photon irradiance (Es cm^{-2} s^{-1})
a = total solution absorbance coefficient (cm^{-1})
z = optical pathlength (cm)

Similarly, indirect photolysis can be modelled by the relationship (Pereira *et al.*, 2007):

$$k'_i = k_{C/OH}[OH]_{ss}$$

Steady-state ●OH concentration $OH_{SS} = \frac{\sum k_s(\lambda)\Phi_{OH}(\lambda)[H_2O_2]}{\sum_i k_{S,OH}[S]_i}$

$\Phi_{OH}(\lambda)$ = ●OH quantum yield from H_2O_2 photolysis
K_s = pseudo-first order rate constant for ●OH scavenging terms (s^{-1})

In practice, the OH radical rate constant of a specific chemical contaminant may be determined by competition kinetics experiments using reactants that are known not to undergo significant direct photolysis such as nitrobenzene (Wu *et al.*, 2007) or para-Chlorobenzoic acid (pCBA) (Pereira *et al.*, 2007).

AOPs widen the range of organic chemicals that may be oxidised as well as significantly increase the reaction rates (von Gunten, 2003). Once generated, hydroxyl radicals can attack organic molecules by a number of mechanisms including radical addition, hydrogen abstraction, electron transfer and radical combination. Detailed reaction kinetics for UV-AOP degradation of a range of chemical contaminants including pharmaceuticals (Pereira *et al.*, 2007), and pesticides (Wu *et al.*, 2007) have been reported. Under suitable conditions, the reaction of hydroxyl radicals with organic chemicals may proceed to complete oxidation to produce water, carbon dioxide and salts. This process is known as mineralisation.

In an ozone AOP, oxidative degradation of organic chemicals can occur either by direct reaction with molecular ozone (O_3) or via the formed hydroxyl radicals (Staehelin & Hoigne, 1985). The relative dominance of the actual oxidative pathway will depend on the ratio of molecular ozone and hydroxyl radicals, and the corresponding reaction kinetics (Elovitz *et al.*, 2000; von Gunten, 2003).

The overall extent of oxidation for any AOP is dependant on the contact time and the concentration of scavengers in the water (ie non-target oxidisable species) (Chen *et al.*, 2007b). Typically, dissolved organic carbon (DOC) and carbonate/bicarbonate are the most important scavengers in drinking waters (Wu *et al.*, 2007). High concentrations of DOC and carbonate/bicarbonate can render mineralisation of chemical micropollutants quite inefficient and very costly (von Gunten, 2003). However, pre-treatment processes such as GAC or RO significantly reduce DOC concentrations, thus enhancing oxidation efficiency.

Water quality and dissolved composition may serve to either enhance or suppress degradation rates of individual contaminants by UV/H_2O_2 and UV processes (Shemer & Linden, 2007). In order

to better-predict likely impacts, a new concept was recently introduced to determine and characterise the overall hydroxyl radical scavenging potential of a particular water matrix (Rosenfeldt & Linden, 2007). The improved understanding of this matrix scavenging factor can be expected to have significant implications for future risk assessment activities and determination of appropriate treatment plant operating conditions.

Direct UV photolysis of some endocrine disrupting chemicals such as bisphenol A (BPA), estradiol (E2) and ethinylestradiol (EE2) has been investigated using both monochromatic (254 nm) low pressure UV lamps, and polychromatic medium pressure UV lamps (Rosenfeldt & Linden, 2004; Chen *et al.*, 2006a; Chen *et al.*, 2007a; Rosenfeldt *et al.*, 2007). These studies have revealed that without enhanced hydroxyl radical formation, medium pressure lamps are required for effective degradation of these chemicals. However, in all cases, the EDCs were even more effectively degraded using UV/H_2O_2 advanced oxidation than by direct UV photolysis.

Similarly, the oxidation of some chemical contaminants in secondary treated effluents by direct application of molecular ozone is an effective process. For example, many pharmaceuticals, estrogenic hormones and volatile organic chemicals (VOCs) can be oxidised to more than 90-99% using typical ozone treatment doses (Ternes *et al.*, 2003; Huber *et al.*, 2005; Irmak *et al.*, 2005; Westerhoff *et al.*, 2005; Chen *et al.*, 2006b). Typical doses depend on the initial water quality, but are normally calculated to achieve a residual of 0.2-0.3 mg/L after 3 min of contact time and zero residual within 10 min (von Gunten, 2003; Westerhoff *et al.*, 2005). However, advanced oxidation utilising hydrogen peroxide is a more effective process for an even wider range of these target species (Zwiener & Frimmel, 2000; Huber *et al.*, 2003; von Gunten, 2003; Chen *et al.*, 2006b).

Advanced oxidation is often relied upon to degrade chemicals which may not be well removed by reverse osmosis. Two important examples are NDMA (Mitch *et al.*, 2003) and 1,4-dioxane (Zenker *et al.*, 2003).

There are a number of possible sources of NDMA in treated effluent including contamination of source wastewater by industrial discharges (Sedlak & Kavanaugh, 2006). However, an important possible source for IPR is its formation during chloramination processes used for membrane biofouling control (Mitch & Sedlak, 2002). Effective removal of NDMA can be achieved by UV photolysis with a typical dose of 1000 mJ/cm^2 (Stefan & Bolton, 2002; Mitch *et al.*, 2003; Sedlak & Kavanaugh, 2006). Low pressure UV lamps emitting mainly monochromatic light at 254 nm, medium-pressure lamps emitting polychromatic light and pulsed UV systems have all been used for NDMA removal (Mitch *et al.*, 2003; Sedlak & Kavanaugh, 2006). UV treatment was added to the Orange County Water District scheme for the removal of NDMA in 2000/2001 (OCWD, 2000).

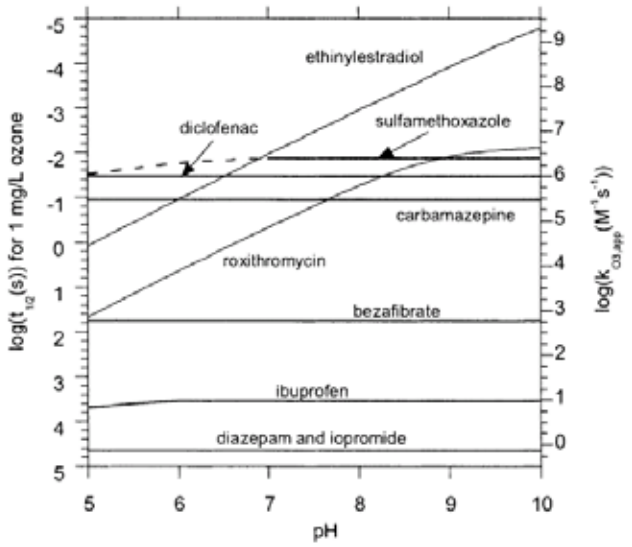
UV doses required for NDMA destruction (1000 mJ/cm^2) are approximately an order of magnitude higher than those for virus removal (Sedlak & Kavanaugh, 2006). The electrical energy required for this oxidation is expressed in EE/O units, defined as the electrical energy input per unit volume per log order of reduction (Metcalf & Eddy. Inc., 2003). Based on currently available technology, the required EE/O value for NDMA is in the order of 21 to 265 kWh/10^{3}m^{3}log order with a 5 to 6 mg/L dose of H_2O_2 (Soroushian *et al.*, 2001). However, in the case of NDMA treatment post RO, the addition of H_2O_2 is considered to be somewhat redundant since UV radiation alone is highly effective (Sharpless & Linden, 2003; Sedlak & Kavanaugh, 2006).

The chemical 1,4-Dioxane is mainly used as an industrial solvent and as a solvent stabilising agent (Zenker *et al.*, 2003). It is also present in many household surfactants and some fractions of these products ultimately end up in wastewater treatment plant influent. 1,4-Dioxane is efficiently mineralised by advanced oxidation with UV/H_2O_2 (Maurino *et al.*, 1997; Stefan & Bolton, 1998). Advanced oxidation with ozone/H_2O_2 can also be used to degrade 1,4-dioxane (Adams *et al.*, 1994).

Experimentally determined half-lives and second-order rates constants for the reactions of some selected pharmaceuticals with molecular ozone as a function of pH are presented in Figure 3-7 (Huber *et al.*, 2003). These half-lives were calculated for an ozone concentration of 1 mg/L and do

not include reactions with hydroxyl radicals. As for UV AOPs, the generation of hydroxyl radicals raises rate constants to the order of 10^9-10^{10} $M^{-1}s^{-1}$ (Huber *et al.*, 2003).

Figure 3-7: Half-lives and apparent second-order rate constants for the reactions of pharmaceuticals with ozone as a function of pH at 20 °C (Huber *et al.*, 2003).



Unless mineralisation is achieved by advanced oxidation of highly pre-treated water, many chemical contaminants will form degradation products which will persist in the water (Wu *et al.*, 2007). These byproducts are typically polar soluble chemicals such as phenols, quinones and acids, and may be more toxic than their parent chemical compounds (Shemer & Linden, 2007). They are often further removed by biodegradative (Yavich & Masten, 2003; Yavich *et al.*, 2004) or coagulation (Chaiket *et al.*, 2002; Singer *et al.*, 2003) processes. However, investigations on some active pharmaceuticals such as ethynylestradiol (Huber *et al.*, 2004) and carbamazepine (McDowell *et al.*, 2005) have shown that even partial oxidation is sufficient to reduce pharmacological activity and toxicity of these agents.

A recent comparison of low pressure and high pressure UV lamps with ozone for the production of hydroxyl radicals concluded that although the comparison is complex, ozone is commonly the more energy efficient means of production (Rosenfeldt *et al.*, 2006). Although energy costs are a key component of comparing available technologies, other important considerations include issues related to chemical storage, handling and pumping, reactor footprint, and potential byproduct formation.

3.4.1.4 Ion Exchange processes

Ion exchange (IX) systems can be used to remove both anionic (eg. NO_3^-) and cationic (eg. NH_4^+) forms of nitrogen. Some forms of non-ionic nitrogen may be removed by ion exchange by using strong acids or bases to convert them into either cationic or anionic species. The ion exchange process works by exchanging an ion of similar charge for the target cation or anion. For the nitrate (NO_3^-) removal process, anion exchange resins are used that exchange chloride ions for nitrate and sulphate ions in the water as it passes through the resin. Since most anion exchange resins have a higher selectivity for sulphate than nitrate, the level of sulphate in the water is an important factor in the efficiency of an ion exchange system for removing nitrates. Cationic ammonia (NH_4^+) can be removed with either a strong acid cation exchange resin or a weak acid

cation exchange resin. Clinoptilolite, a naturally occurring zeolite that has excellent selectivity for ammonium over most other cations in wastewater, can be used as an exchange medium. A weak acid cation exchange resin will only work when the ammonia is present as the free base. When ammonia is present as a salt, a strong acid cation resin is needed to split the salt. Similarly, organic nitrogen needs to be protonated or oxidised prior to the IX process to exchange for a cation.

Ion exchange processes work in a multiple batch process until all of the sites on the resin that are available for exchange have been consumed. At this point the process is stopped and the resin is regenerated using a strong acid or base solution and the retained nitrogen is discharged in the spent regeneration solution. Ion exchange systems have been used in water recycling plants at the Upper Occoquan Sewage Authority. Recycled water produced at this facility is discharged into the Occoquan reservoir which provides up to 40% of the potable water for the Washington DC. In the event that concentrations of nitrate reach 50% of the drinking water MCL at the Fairfax county drinking water treatment plant intake which is located downstream from the recycling plant on the Occoquan reservoir the recycled water is processed through the ion exchange beds to reduce the total nitrogen to less than 5 mg/L (as N).

3.4.2 General removal efficacy of organic contaminant – Membrane filtration

Membrane rejection of chemical contaminants is ultimately determined by complex interactions of electrostatic and other physical forces acting between a specific solute (chemical contaminant), the solution (water and other solutes present), and the membrane itself. The nature of these forces is dependent on numerous physical properties of the solute, solution and membrane.

A useful guide for the classification of chemical contaminants for removal estimation has been proposed by Bellona et al. (2004). This system was derived as the result of a comprehensive review of published studies reporting variable rejection behaviour of a wide range of solutes by various commercially available membranes. The important molecular factors determining rejection are presented in Figure 3-8. These include;

- Molecular size: The size of a molecule is often approximated by reference to its molecular weight (MW), but can be more accurately described in terms of its molecular diameter and molecular width (MWd).

- Electrostatic properties: The electrical charge of a molecule is related to how acidic it is. This is commonly described by an acid dissociation constant (pKa) and its relationship to the overall acidity of the water (pH).

- Polarity or hydrophobicity: The 'polarity' of a molecule determines whether it is generally very soluble in water or would prefer to partition to non-water phases. Molecules that tend to partition away from water are said to be 'hydrophobic'. The degree of hydrophobicity is commonly described by an 'octanol-water partitioning coefficient' (log K_{ow}).

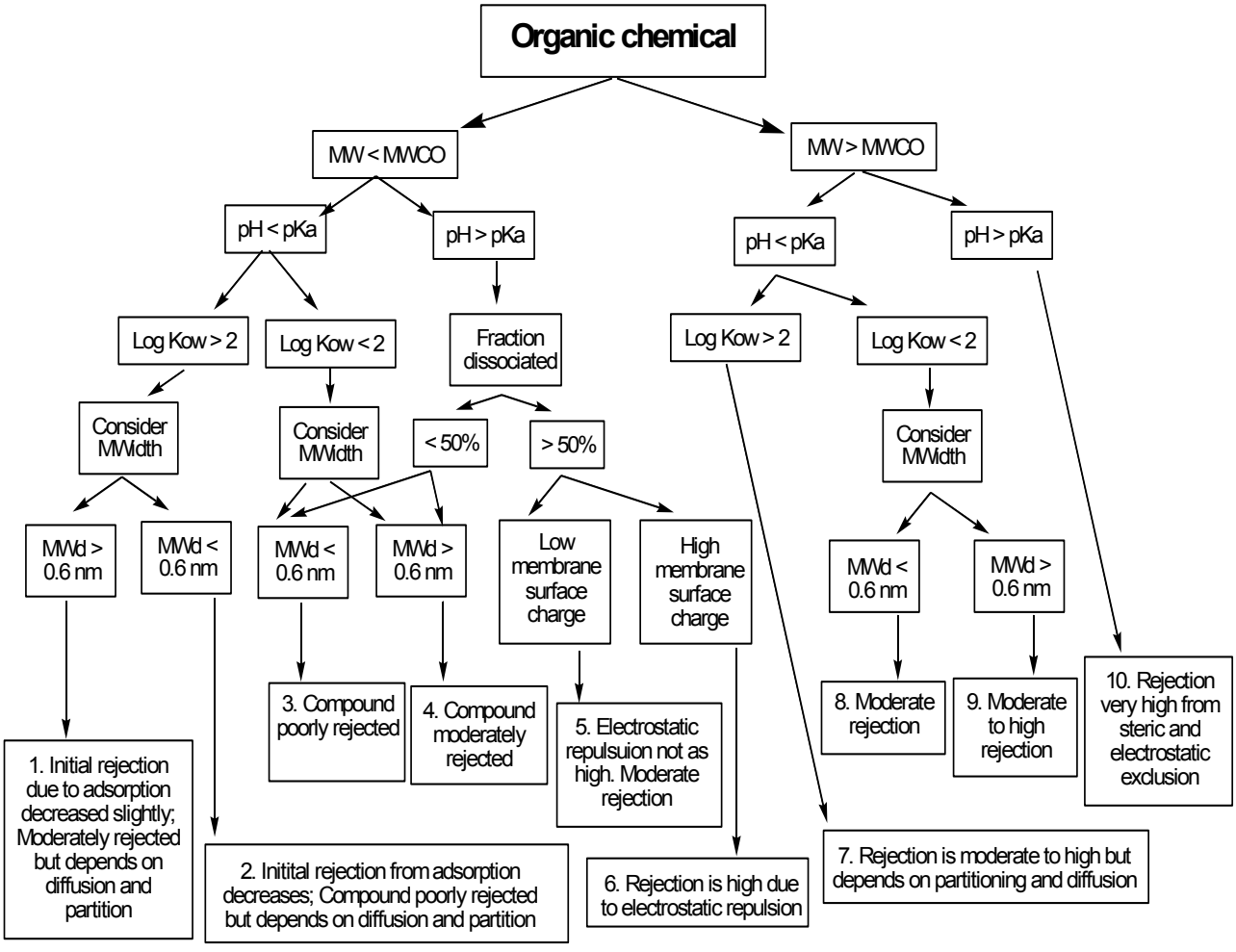
The three mechanisms by which a molecule may be rejected by the reverse osmosis membrane are size exclusions (or sieving), electrostatic repulsion and hydrophobic adsorption.

The most fundamental of the rejection mechanisms is size exclusion. This is a sieving process for which molecular size or geometry prevents large molecules from passing through the dense molecular structure presented by the active surface of the membrane. Size exclusion is believed to be the dominant retention mechanism for relatively large molecules such as surfactants, hormones, most pharmaceuticals, proteins and other molecules with MW greater than 200 atomic mass units (or g/mol) by reverse osmosis membranes (Schäfer et al., 2003; Drewes et al., 2006). However, commercial membranes vary in terms of their ability to reject molecules by size exclusion. Their ability to do so is often described by the membranes Molecular Weight Cut-Off (MWCO). This is the manufacturers rating of the ability of the membrane to reject an uncharged dextran (sugar) based on molecular weight. Membranes with a low MWCO are commonly referred

to as 'tight' membranes compared to those with a higher MWCO, referred to as 'loose' membranes.

Experiments with looser membranes (nanofiltration, ultrafiltration and microfiltration), have revealed that under some conditions, some chemicals are prevented from permeating the membrane due largely to adsorption onto the membrane surface (Schäfer et al., 2003; Yoon et al., 2006). This adsorption is believed to be due to hydrophobic interactions between relatively non-polar solutes and membranes. Such adsorptive removal may be less reliable than removal based purely on size exclusion since variations in solution pH lead to variations in hydrophobicity, and possible saturation of adsorption sites may limit total adsorption capacity if the membranes are not routinely cleaned (Nghiem & Schafer, 2006a).

Figure 3-8: Rejection diagram for chemical micropollutants during membrane treatment based on solute and membrane properties (Bellona *et al.*, 2004). MW=molecular weight, pKa= acid dissociation constant, Log Kow = logarithm of octanol-water partitioning coefficient, MWd=molecular width, MWCO=molecular weight cut-off.



An example of how the rejection diagram in Figure 3-8 may be used to describe the removal efficiency for molecules that are commonly found in wastewater is presented in Table 3-3. The

predictions derived from the rejection diagram were determined assuming the use of a high surface-charge RO membrane with MWCO of 100 at pH 7. These predictions are qualitatively consistent with recent findings from groundwater treatment and water recycling plants where molecules such as monochloramine, NDMA and 1,4-dioxane are poorly removed by reverse osmosis membranes.

Table 3-3: Predicted RO rejection categories of some organic chemicals based on molecular properties. Rejection category is described in Figure 3-8.

Organic chemical	Classification	MW	pKa	log Kow	MWd > 0.6 nm	Rejection category*
1,2-Dichloroethane	organic solvent	98.96	nil	1.48	n	3
1,4-Dioxane	organic solvent	88.10	nil	-0.27	n	3
2-Naphthol	pigment intermediate	144.17	9.57	2.73	n	7
Acetic acid	natural product	60.05	4.79	-0.29	n	6
Acetylsalicyclic acid	pharmaceutical	180.16	3.48	1.19	n	10
Acrylonitrile	industrial product	53.06	nil	0.25	n	3
Aldrin	pesticide	364.92	nil	6.5	n	7
Benzene	organic solvent	78.11	nil	2.13	n	2
Bromoform	disinfection by-product	252.73	nil	2.42	n	7
Caffeine	stimulant	194.19	12.61	-0.081	y	9
Carbamazepine	pharmaceutical	236.27	13.94	2.673	n	7
Carbon Tetrachloride	disinfection by-product	153.82	nil	2.83	n	7
Chloroform	disinfection by-product	119.38	nil	1.97	n	8
Clofibric acid	pharmaceutical	214.65	3.18	2.724	n	10
Dichloroacetic acid	disinfection by-product	128.94	1.37	0.54	n	10
Dichloromethane	disinfection by-product	84.93	nil	1.25	n	3
Dichlorprop	pesticide	235.06	3.03	2.945	n	10
Diclofenac	pharmaceutical	296.15	4.18	3.284	n	10
Dieldrin	pesticide	380.91	nil	5.4	n	7
Estradiol	hormone	272.39	10.27	4.01	n	7
Estrone	hormone	270.37	10.25	3.13	n	7
Ethinylestradiol	hormone	296.41	10.2	3.67	n	7
Fenofibrate	pharmaceutical	360.83	nil	4.804	n	7
Gemfibrozil	pharmaceutical	250.33	4.75	4.387	y	10
Glucose	natural product	180.16	12.45	-3.17	n	8
Glutaric acid	natural product	132	4.33	-1.04	n	10
Ibuprofen	pharmaceutical	206.28	4.41	3.722	n	10
Ketoprofen	pharmaceutical	254.28	4.23	2.814	n	10
Mecoprop	pesticide	214.65	3.18	2.835	n	10
Monochloramine	disinfection by-product	51.48	nil	-1.19	n	3
Naphthalene	CCL	128.2	nil	3.3	n	7
Naproxen	pharmaceutical	230.26	4.4	2.998	n	10
NDMA	disinfection by-product	74.08	nil	0.57	n	3
Nonylphenol	surfactant product	220.36	10.14	5.76	n	7
Octylphenol	surfactant product	206.33	10.15	5.5	n	7
Phenacetine	pharmaceutical	179.22	nil	1.626	n	8
Primidone	pharmaceutical	218.25	12.26	-0.844	n	8
Propyphenazone	pharmaceutical	230.31	2.37	1.737	n	10
Salicylic acid	pharmaceutical	138.12	3.01	2.061	n	10
Sucrose	natural product	342.3	12.81	-3.85	n	8
Testosterone	hormone	288.42	nil	3.48	n	7
Trichloracetic acid	disinfection by-product	163.39	1.1	1.67	n	10
Trichloroethylene	organic solvent	131.39	nil	2.42	n	7
Tris(2-chloroethyl)-phosphate	flame retardant	285.49	nil	0.48	n	8
Tris(2-chloroisopropyl)-phosphate	flame retardant	327.57	nil	1.53	y	9
Urea	natural product	60.06	13.9	-2.11	n	3

*Refer to Figure 3-8.

The final concentration of molecules in the RO permeate is highly dependant on the configuration of the membrane, the type of membrane, the membrane surface charge and the MWCO. Other important factors that contribute to rejection include the type of spacer material used to form the membrane feed channels and the system operating conditions including pressure, flux and pH. All these factors determine the concentration of the molecules at the surface of the membrane and the subsequent transport or rejection of the molecules across the membrane based on the physical-chemical properties described in Figure 3-8. For this reason rejection data determined in simple laboratory-scale experiments should be interpreted cautiously before drawing conclusions on full scale plant performance because the conditions under which the membranes operate will be different.

During normal operation, membranes are prone to fouling by the build-up of precipitated chemicals or, in the case of IPR, by the growth of microbial biomass (Oschmann *et al.*, 2005; Nghiem *et al.*, 2006; Nghiem & Schafer, 2006b). Fouling can lead to significant changes in membrane surface properties and thus in the way in which they interact with water and solutes (Nghiem *et al.*, 2007). In many cases, fouling is regarded as a hindrance since it decreases membrane porosity and thus requires elevated pressures to maintain operational flux. However, recent investigations reveal that fouling can also lead to improved rejection of many solutes (Drewes *et al.*, 2006; Schafer *et al.*, 2006; Xu *et al.*, 2006). This observation is believed to be due to increased negative surface charge leading to increased electrostatic rejection of ionic species; along with simultaneously increased adsorptive capacity for non-ionic solutes (Xu *et al.*, 2006). Most previous studies reporting relationships between physical-chemical properties of solutes and membrane interactions have been conducted using unfouled 'virgin' membranes and thus their conclusions are unlikely to be quantitatively extendable to full-scale systems subjected to long-term operation (Agenson *et al.*, 2003; Schäfer *et al.*, 2003; Nghiem *et al.*, 2004; Nghiem *et al.*, 2005). Indeed, many of these studies were used in the derivation of the rejection diagram (Figure 3-8) by Bellona *et al.* (2004) and this must be seen as a limitation to its current usefulness for predicting chemical behaviour in real full-scale treatment systems.

Manufacturers of RO membranes routinely provide fact sheets indicating a percentage rejection that should be achieved for a range of chemicals. However, because of variable plant design and operating conditions, preliminary performance testing should be undertaken for any new IPR scheme, either in pilot-scale or the full-scale plant prior to the augmentation of drinking water supplies. For example, a study of pharmaceutical and estrogenic hormone removal was undertaken at an advanced water recycling demonstration plant in Queensland (Khan *et al.*, 2004). This study involved spiking unnaturally high concentrations of the selected chemicals into the influents of various stages of the treatment train to test performance. In the case of reverse osmosis, a single membrane module was used and was shown to be the most effective barrier for the removal of the investigated chemicals. Studies of these chemicals in full-scale operational reverse osmosis plants are limited due to the fact that concentrations are generally already very low prior to membrane treatment and such 'spiking' experiments are unlikely to be permitted by regulatory authorities or plant operators. However, a recent study undertaken at two full-scale reverse osmosis plants in the USA identified numerous pharmaceuticals in the RO feed waters (Drewes *et al.*, 2005). The permeate water from this plant did not reveal any quantifiable detections except for low concentrations of caffeine at one facility. In other words, the pharmaceuticals were completely removed by the RO membrane, as best as the sensitivity of the analytical method could determine.

In additional studies performed at California's Water Factory 21 in the mid 1990's, thin film composite RO membranes were shown to be very effective at removing the so called "wastewater signature compounds". These are derivatives of chemicals that are commonly used in foods and detergents, and include ethylenediamine tetraacetic acid (EDTA) and the structurally similar, but slightly more biodegradable, nitrilotriacetic acid (NTA). Both chemicals are chelating agents and phosphate substitutes used as stabilisers in detergents. EDTA and NTA are present in raw

wastewater and persist through the biological treatment process. Other wastewater indicators include the alkylphenol polyethoxcy carboxylates (APEC), formed by biodegradation and/or carboxylation of alkylphenol polyethoxylates (APEO), a class of non ionic surfactants, in the wastewater treatment process. An example of the use of these chemicals during the treatment of water from the Santa Ana River is provided in Table 3-4. While they are measurable at up to 70 µg/L after microfiltration, they are reduced below the detection limit of 0.1 µg/L by the reverse osmosis membrane.

Table 3-4: Removal of wastewater indicator chemicals by thin film composite reverse osmosis (Reinhardt, 1996).

	After microfiltration	After reverse osmosis
Ethylenediaminetetraacetic acid	65 +/- 27µg/L	ND
Nitrilotriacetic acid	1.6 +/- 27 µg/L	ND
Alkylphenol polyethoxcy carboxylates	59 +/- 30 µg/L	ND

ND = Not detected

Pilot tests and demonstration studies on membrane pre-treatment systems and new reverse osmosis membranes in the 1990's facilitated the expansion of the original Water Factory 21 under a scheme called the Groundwater Replenishment (GWR) System. The GWR System will increase the capacity of WF21 from 60,000 m^3/day to 266,000 m^3/day by replacing the high-pH lime process with membrane filtration as a pre-treatment to reverse osmosis. The GWR scheme will be commissioned in 2007, however, a 20,000 m^3/day interim Water Factory was commissioned in 2004 to maintain flow to the existing seawater intrusion barrier following the demolition of the original Water Factory 21. The operation of the interim Water Factory between 2004 and 2006 allowed for chemical analysis of the AWT process consisting of microfiltration followed by reverse osmosis and advanced oxidation. The results of this testing were reported by Daugherty *et al.* (2005). After advanced water treatment comprising microfiltration, reverse osmosis and ultraviolet irradiation, all analysed chemicals were significantly below permit requirements and the vast majority were below reportable detection limits. For example, the 12 volatile organic chemicals (VOCs) analysed were all below reportable detection limits of 0.1-0.5 µg/L. The 17 non-volatile synthetic organic chemicals were all below reportable detection limits of 0.1 to 2 µg/L. The chlorine disinfection by-products 'total trihalomethanes' were observed at 0.2 µg/L compared to a permit requirement of 80 µg/L, while all other disinfection byproducts (haloacetic acids, bromate and chlorate) were not detected. Nine of the 10 measured unregulated chemicals could not be detected, however boron was the exception and was reported to be 0.28 mg/L, below the Department of Health Services 'action level' of 1 mg/L. The results of analysis of EPA Priority Pollutants, as well as some additional chemicals selected for analysis are presented in Table 3-5.

Table 3-5: EPA Priority Pollutants and additional chemicals analysed at Phase 1 Groundwater Replenishment Scheme, Orange County Water District (Daugherty *et al.*, 2005)

Chemical	Category	Result (detection limit)
N-Nitrosodi-N-proylamine	EPA Priority Pollutant	N.D. (<5 µg/L)
N-Nitrosodiphenylamine	EPA Priority Pollutant	N.D. (<5 µg/L)
Aldrin	EPA Priority Pollutant	N.D. (<0.03 µg/L)
HCH-alpha (Alpha-BHC)	EPA Priority Pollutant	N.D. (<0.02 µg/L)
HCH-beta (Beta-BHC)	EPA Priority Pollutant	N.D. (<0.02 µg/L)
HCH-delta (Delta-BHC)	EPA Priority Pollutant	N.D. (<0.02 µg/L)
4,4'-DDT	EPA Priority Pollutant	N.D. (<0.01 µg/L)
4,4'-DDE	EPA Priority Pollutant	N.D. (<0.01 µg/L)
4,4'-DDD	EPA Priority Pollutant	N.D. (<0.01 µg/L)
Dieldrin	EPA Priority Pollutant	N.D. (<0.02 µg/L)

Endosulfan I	EPA Priority Pollutant	N.D. (<0.05 µg/L)
Endosulfan II	EPA Priority Pollutant	N.D. (<0.01 µg/L)
Endoulfan sulphate	EPA Priority Pollutant	N.D. (<0.05 µg/L)
Endrin aldehyde	EPA Priority Pollutant	N.D. (<0.1 µg/L)
17α-Ethynylestradiol	Hormone	N.D. (<0.01 µg/L)
17β-estradiol	Hormone	N.D. (<0.01 µg/L)
Estrone	Hormone	N.D. (<0.01 µg/L)
Polybrominated diphenylethers	Flame retardants	N.D. (<0.05 µg/L)
Caffeine	Stimulant	N.D. (<0.1 µg/L)

N.D. = Not detected

3.4.3 Actual removal efficacy based on analysis of data from water recycling plants using probabilistic techniques

The removal efficiency of chemicals in a RO recycling plant and the effect of various parameters on the removal efficiency have been assessed. Feed and permeate data from RO stations situated in the Orange County Water District (OCWD) in California, USA was obtained. The data was stored in the districts Water Quality Records Management System (WRMS). The data was collected by Water Factory 21 operations staff and analyzed in the OCWD main laboratory. The main laboratory is an analytical facility certified by the state of California for water quality analysis. The information was recorded during the period of October 1995 to January 1999 and provided information regarding total organic carbon (TOC) concentrations found in water streams at three sites in the OCWD, Water Factory 21 (WF21), Microfiltration Demonstration Plant (MDP) and RD7 Pilot Plant, related operation details given in Table 3-6.

Table 3-6: Orange County RO filtration stations

Organics Removal Data Base - Reverse Osmosis Equipment Specifications			
Name	**Water Factory 21**	**MDP**	**R&D7**
Year Commissioned	1976	1995	1995
Capacity (m^3/day)	18,900	1900	100
Pretreatment	High-pH lime clarification + media filtration	Microfiltration	Microfiltration
No of trains	4	1	1
Membrane type	Cellulose acetate (CA)	Aromatic polyamide thin film composite (TFC)	Aromatic polyamide thin film composite (TFC)
No of stages	3	3	3
Array configuration	3:2:1	3:2:1	2:1
Recovery	85%	87%	75%
Flux	16 L/m^2/h	20 L/m^2/h	20 L/m^2/h
Data collection (start)	1/12/95	4/8/98*	10/95
Data collection (end)	3/8/97	14/1/99*	7/97
Sample method	Grab sample	Grab sample & on-line	Grab sample
Maintenance/Cleaning History	Yes	Yes	Yes

* Condition data (i.e pH, temperature) available from 8/96 to 10/99

The data in Table 3-6 were analyzed for the effect of the following paramters on the removal of total organic carbon:

- feed temperature
- membrane type and,
- membrane age

The temperature of the feedwater varied from 19.5°C to 28°C as a function of the time of year (Figure 3-10).

Figure 3-9: MDP feed temperature variation vs TOC rejection

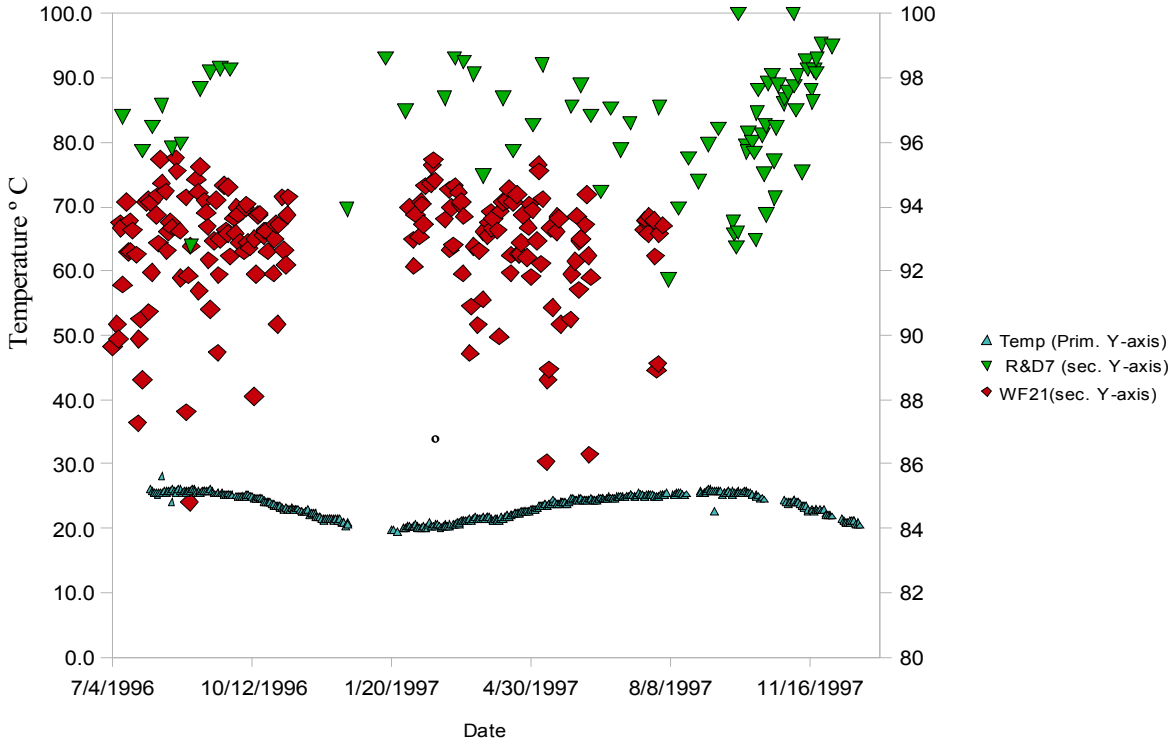


Table 3-7: Seasonal TOC rejection variation

Site	Time Period	Mean Temperature (°C)	No of observations	Mean TOC rejection (%)	Standard Deviation
WF21	Max, Summer	25.6	31*	91.73	2.00
	Min, Winter	20.3	28*	94.05	0.91
R&D7	Max, Summer	25.6	4**	97.27	2.24
	Min, Winter	20.3	3**	97.23	0.50

* Daily observations made during the summer and winter
** Weekly observations made during the summer and winter.

The effect of temperature on TOC removal was less pronounced for thin film composite membranes (R&D7) compared with cellulose acetate membranes (WF21) Table 3-7. Removal of TOC by the cellulose acetate membranes was greater during the colder months than the warmer months. In contrast, organics removal by the TFC was mostly independed of temperature (Figure 3-9).

Figure 3-10: Feed and permeate TOC concentrations of RD7 and WF21 RO plants

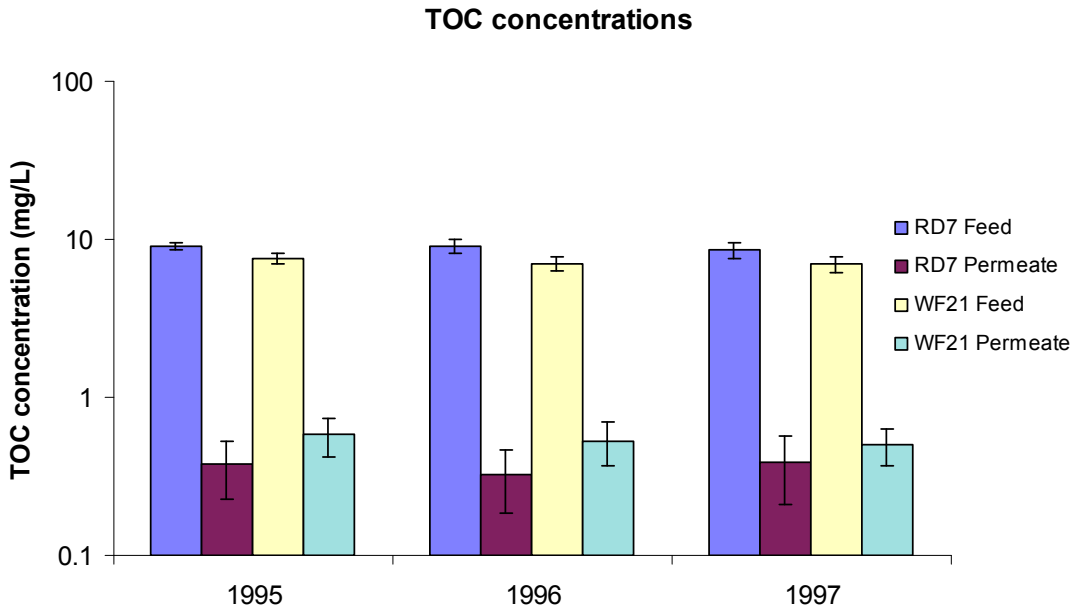
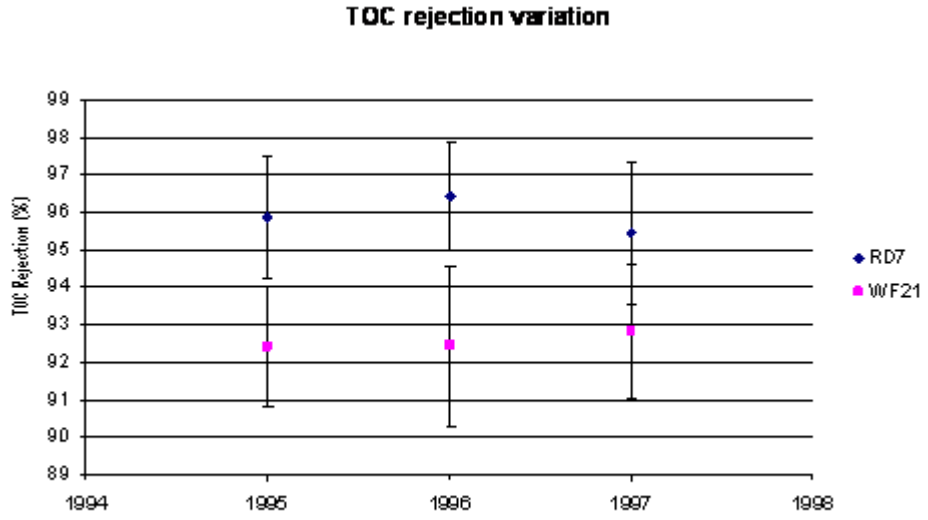


Figure 3-10 illustrates that even though the RD7 station has a slightly more concentrated feed, generally the permeate solutions had a lower TOC content than the corresponding WF21 permeate each year. Consequently, the average TOC removal efficiency of the TFC and the CA membranes accounting for annual temperature variations was effectively stable in the study period of 1995 to 1998.

Figure 3-11: TOC rejection variations due to membrane difference



The study at WF21 demonstrated that the average total organic carbon removal of the TFC membranes was higher than the cellulose acetate membranes. For the TFC membranes the average TOC rejection was 96.08 with a standard deviation of 1.64. This was compared with the TOC organic rejection of the cellulose acetate membranes which was found to be 92.66 with a standard deviation of 2.03. As such, it can be seen that polyamide thin film composite membranes provide greater organic removal efficacy compared to the cellulose acetate variety. Consequently, thin film composite membranes are now the preferred membrane for IPR applications.

3.4.4 Reliability of treatment removal efficacy based on analysis of temporal data from water recycling plants

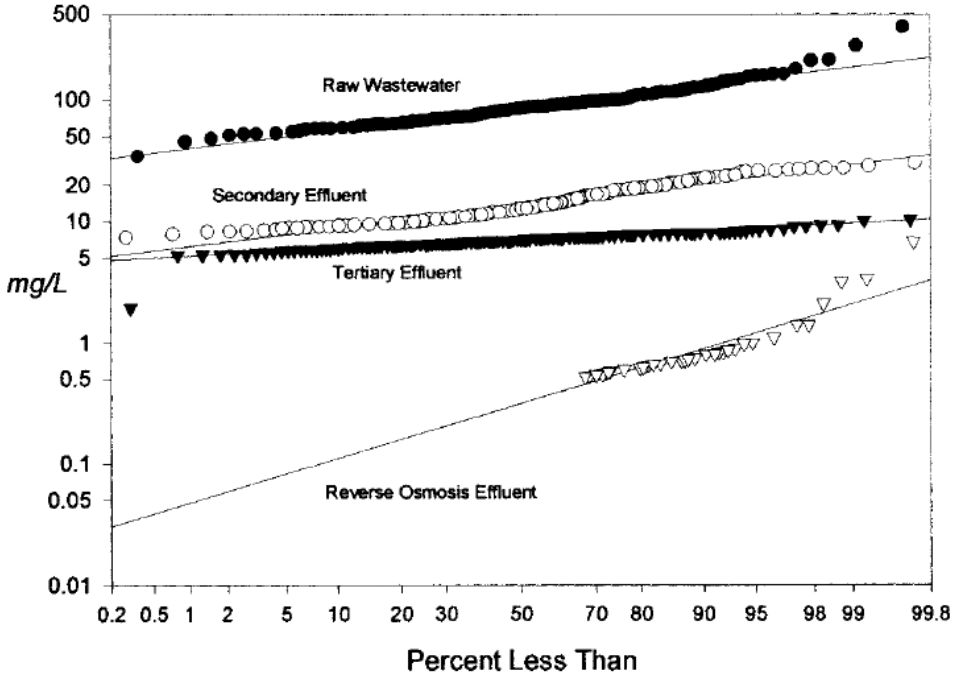
A protocol for the evaluation of water and wastewater treatment plant reliability has been proposed by Eisenberg et al (2001). This includes a methodical evaluation of mechanical reliability and plant performance (variability). The methodology relies on a range of measurements and observations to characterise treatment facility reliability with respect to:

1. variability of treatment effectiveness under normal operation
2. probability of mechanical failures
3. impacts of observed or projected mechanical failures upon final water quality.

The methodology allows for the use of individual process performance data to make an estimation of overall treatment reliability for the entire facility. This is essential for constituents which may normally be removed to levels that are below levels of detection in the treatment plant effluent.

The evaluation of treatment variability under normal operation may be achieved by summarising observed water quality using basic statistical tools associated with frequency analysis (means, standard deviations, etc). The overall system variability may be characterised by estimating the cumulative probability distributions associated with individual chemical contaminants at key treatment units throughout the facility. These probability distributions allow the estimation of probability that treatment goals would be exceeded. Eisenberg et al (2001) recommend the assumption of a lognormal distribution for contaminant variability. Water quality variability may then be characterised by the construction of lognormal cumulative probability plots, such as the one shown for TOC in Figure 3-12 (Eisenberg *et al.*, 2001).

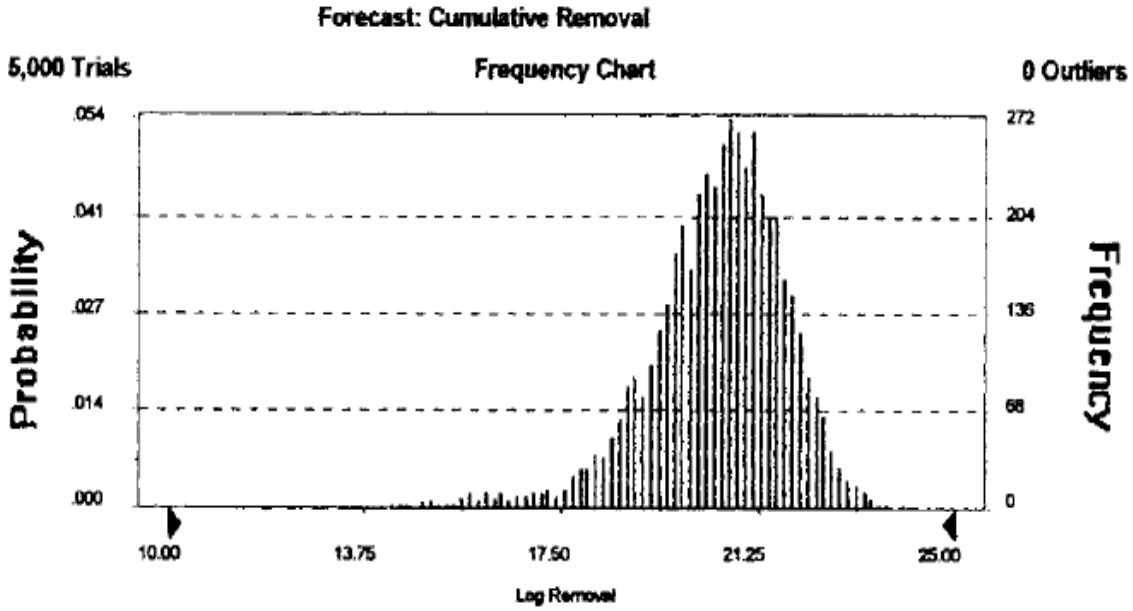
Figure 3-12: Log normal cumulative probability plot for TOC after various treatment processes (Eisenberg *et al.*, 2001).



As can be observed from Figure 3-12, TOC levels in raw wastewater from this plant could be expected to range between 30 – 500 mg/L, secondary effluent 7-20 mg/L, and tertiary effluent (treatment involves ferric alum coagulation followed by media filtration) 2-7 mg/L. 70 per cent of the data for reverse osmosis effluent were reported to be below detectable limits (0.5 mg/L) and 99% were below 1 mg/L. The reverse osmosis data demonstrate the use of this kind of analysis to estimate the distribution of treatment plant performance when a large percentage of data are below detection limits. Such procedure allows for the estimation of summary statistics such as mean and standard deviation for largely unobserved data.

The overall performance distribution of a multiple barrier system may be estimated using consequence frequency assessment methodology analogous to procedures which have become increasingly accepted for quantitative microbial risk assessment (QMRA) (Haas *et al.*, 1999; Haas & Eisenberg, 2001). The concentration of a given contaminant at each stage of treatment is described mathematically as a conditional probability density function. A useful approach is then to employ a Monte Carlo simulation procedure (Burmaster & Anderson, 1994). This requires fitting distributions to the removal of a particular contaminant across each treatment unit, sampling each distribution repeatedly, and computing the final concentration for each set of random samples. By this approach, the plant performance may be represented in a probabilistic manner which explicitly acknowledges both the uncertainty and the variability of the underlying data. An example of the type of cumulative removal that may be forecast is presented in Figure 3-13.

Figure 3-13: Result of consequence frequency assessment for the removal of a contaminant through an AWT (Eisenberg *et al.*, 2001).



The mechanical reliability of a water treatment system can be assessed by the identification of key pieces of equipment in the plant whose failures may be related to effluent quality. The operational availability and maintainability of all treatment units and key components are then determined.

The mechanical reliability assessment can be undertaken by the use of a Critical Component Analysis methodology developed after methods described in US EPA guidance documents (Shultz & Parr, 1982). The Critical Component Analysis is carried out by creating a list of all components in the facility and then categorising the components by treatment unit, component and subcomponent. Data is collected for all planned and unplanned maintenance events. This data is aggregated and then used to compute performance statistics for treatment units and for individual components in the treatment system. The performance statistics describe the expected time between failures for treatment units, the overall mean time between failures of components, and the fraction of time that a unit or component was operating, either including or excluding preventative maintenance. An example of the type of data that may be accumulated are presented in Table 3-8 (Eisenberg *et al.*, 2001).

Table 3-8: Plant performance statistics for mechanical reliability (Eisenberg *et al.*, 2001).

Treatment unit	Number of maint. events[1]	Number of unplanned events[2]	ETBF (days)[3]	Operating availability[4]
Headworks	16	13	26	0.9953
Primary	36	28	41	0.9985
Secondary	82	40	9	0.9757
Tertiary	30	27	13	0.9994
UV	1	1	212	0.9991
Reverse Osmosis	55	35	10	0.9990

[1]Number of times repairs were made including scheduled maintenance on components within the given unit
[2]Number of times repairs were made due to component failure within the unit
[3]Expected time between failure somewhere in the unit process, based on chi-square distribution
[4]Fraction of the study period that all components in the unit were operating.

The data in Table 3-8 indicates that there were a number of planned and unplanned maintenance events on each unit process. The expected time between failures within the unit processes varied between 9 and 212 days. The operating availability, defined as the fraction of the study period that all components in the unit were operating for each of the treatment units was greater than 0.97. Eisenberg *et al*, (2001) conclude that all treatment units were operational more than 97 per cent of the time and that neither component maintenance nor failure caused a significant interruption in the operation of the overall plant.

This type of analysis provides a foundation from which an assessment of the inherent reliability of a treatment system may be made. For example, if it can be demonstrated that a treatment facility is operational nearly 100 per cent of the time on a long-term basis, plant performance data (as described above) may be used to evaluate the probability that the effluent will meet a specified set of criteria. Otherwise, it may be necessary to investigate if and/or how component failures impact treatment plant effluent quality.

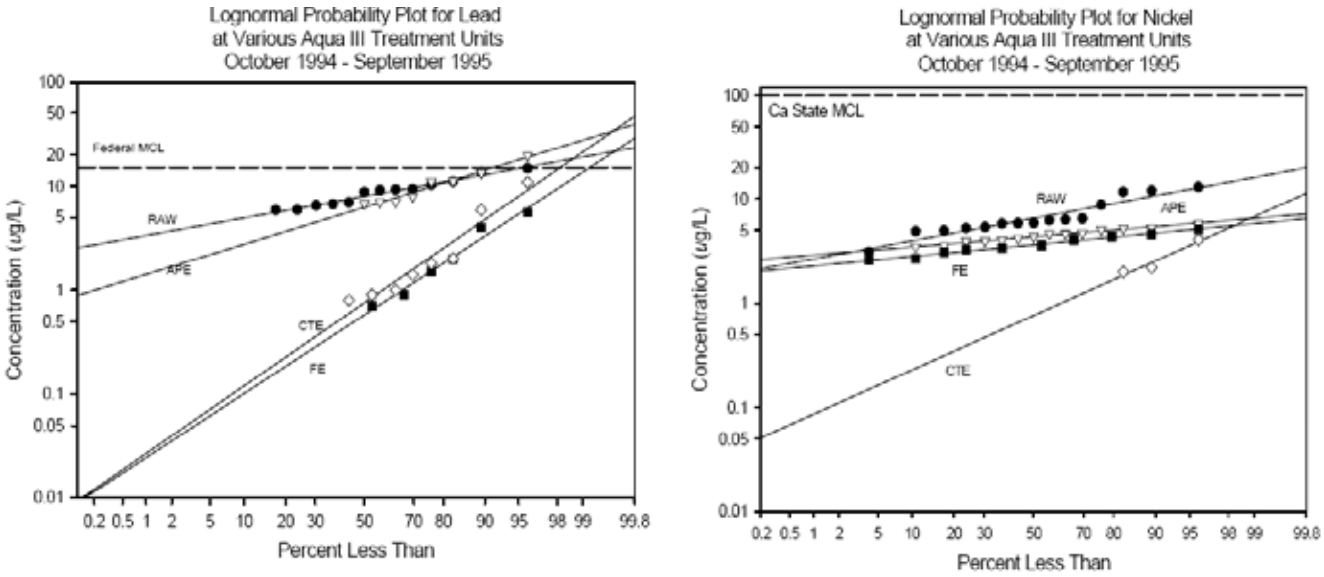
Case Study: San Diego Aqua III

A pilot scale advanced water treatment plant (AWT) was constructed and intensively investigated in the City of San Diego during the 1990s. This scheme, known as the Aqua III AWT, was subjected to a comprehensive suite of health effects studies (Thompson *et al.*, 1992; Western Consortium for Public Health, 1992; de Peyster *et al.*, 1993; Olivieri *et al.*, 1996). Furthermore, a comprehensive reliability analysis of the plant was undertaken and reported by Eisenberg *et al.* (1998).

The reliability of the Aqua III AWT was evaluated in terms of the facility's ability to produce a consistent water quality (plant performance) and the probability of failure of mechanical components (mechanical availability).

The plant performance was assessed in terms of physical parameters, nitrogen compounds, anions, trace and major metals, organic chemical compounds and bacterial indicators. Parametric time series analysis was conducted to identify and investigate trends and periodicity that may have occurred within the collected data at the specific sampling sites. Lognormal probability plots were created for all constituents with sufficient detected data. For example, the lognormal probability plots for lead and nickel concentrations in raw wastewater (RAW), secondary effluent (APE), tertiary effluent (FE), and AWT effluent (CTE) are shown in Figure 3-14 below (Eisenberg *et al.*, 1998).

Figure 3-14: Lognormal probability plots Lead and Nickel at the Aqua III AWT (Eisenberg *et al.*, 1998)



The geometric mean values for both lead and nickel for all unit processes were shown to be well below the corresponding maximum contaminant levels (MCL). Furthermore, the lognormal probability plots demonstrated that the probability that the final plant effluent (CTE) will exceed the MCL was approximately 0.03 for lead and was estimated through extrapolation to be 0.00001 for nickel. The study revealed that the Aqua III AWT produced highly consistent effluent with minimal variation.

The mechanical reliability of the Aqua III AWT was undertaken by determination of the inherent availability (AVI) and the operating availability (AVO). The AVI was used as a measure of the fraction of time that the component or treatment unit could be expected to be operational excluding preventative maintenance downtime. The AVO was used to describe the fraction of the time in which the component or unit was operating.

A statistical analysis was undertaken on the 11 treatment units and the 295 plant components in the Aqua III facility. A summary of the statistical parameters rating mechanical reliability indicated mechanical availability (AVO and AVI) greater than 99 per cent, and that failures within the facility did not affect the overall mechanical reliability of the treatment units.

To investigate the relationship between plant failures and effluent quality, bacteriological indicator monitoring results were correlated to plant component failures. The results indicated that there was no observable association between any specific maintenance procedure or plant failure and the occurrence of indicator microorganism concentrations above the detection limit.

3.4.5 Reliability and Maintainability

The reliability of a system is the ability of the system to perform the required function for a specified period of time. The reliability function, R(t) is defined as the probability that the system will not fail during the stated period of time, t, under stated operating conditions. Some of the commonly used terms to explain the reliability of the system are,

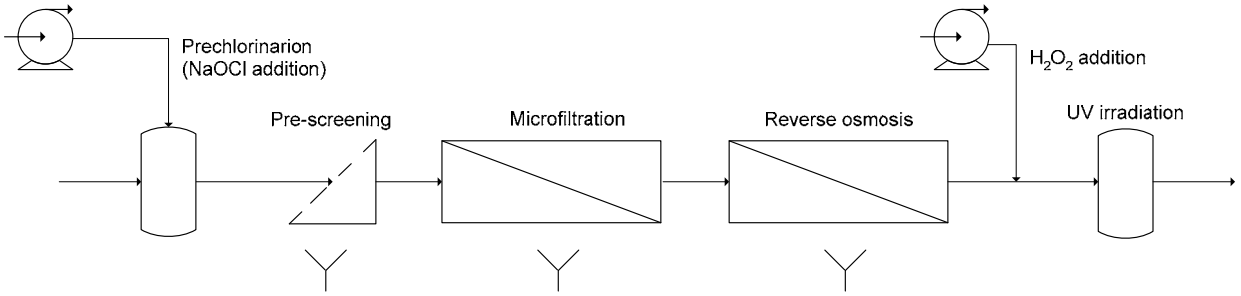
1. Mean time to failure (MTTF): MTTF represents the expectation of the time to failure, which is used as a measure for non-repairable systems.

2. Mean operating time before failures: MTBF represents the expectation of the operating time between failures, it is extremely difficult to predict MTBF for fairly reliable systems, still it can be estimated if the appropriate failure data are available.

3. Mean time to repair (MTTR): MTTR represents the expectation of the time to restoration

The reliability of the advanced water treatment (AWT) plant involves many sub-systems and components whose individual performances affects the performance of the system as a whole. Also the reliability of the whole system is affected by the interaction and configuration of the sub-systems.

Figure 3-15: Advanced Water treatment – process flow diagram



For a typical AWT, the reliability assessment can be derived through the components and weibull distribution parameters. The two weibull parameters, the shape parameter and the scale parameter for a typical AWT based on the process flow diagram shown in Figure 3-15 is tabulated in Table 3-9.

Table 3-9: Weibull distribution parameters for the AWT components

Item	Beta value (β) Weibull shape factor			Eta value (η) Weibull scale factor (characteristic life hours)		
	Low	Typical	High	Low	Typical	High
1. Pre-chlorination						
Cylinders, hydraulic	1	2	3.8	9000000	900000	200000000
Diaphragm, rubber,	0.5	1.1	1.4	50000	60000	300000
gasket, hydraulics	0.5	1.1	1.4	700000	75000	3300000
Valves, recip comp.	0.5	1.4	4	3000	40000	80000
Diaphragm couplings	0.5	2	4	125000	300000	600000
Motors, Ac	0.5	1.2	3	1000	100000	200000
Transmitters	0.5	1	2	100000	150000	1100000
Flow instrumentation	0.5	1	3	100000	125000	10000000
Electro-mechanical parts	0.5	1	3	13000	25000	1000000
2. Pre-screening						
Ball bearing	0.7	1.3	3.5	14000	40000	250000
Sleeve bearing	0.7	1	3	10000	50000	143000
Bolts	0.5	3	10	125000	300000	100000000
Couplings, gear	0.8	2.5	4	25000	75000	1250000
gasket, hydraulics	0.5	1.1	1.4	700000	75000	3300000
Gears	0.5	2	6	33000	75000	500000

	Beta value (β) Weibull shape factor			Eta value (η) Weibull scale factor (characteristic life hours)		
Joints, mechanical	0.5	1.2	6	1400000	150000	10000000
Nuts	0.5	1.1	1.4	14000	50000	500000
Pins	0.5	1.4	5	17000	20000	170000
Springs	0.5	1.1	3	14000	50000	5000000
Motors, Ac	0.5	1.2	3	1000	100000	200000
Controllers, pneumatic	0.5	1.1	2	1000	25000	1000000
Control valves	0.5	1	2	14000	100000	333
Motorised valves	0.5	1.1	3	17000	25000	1000000
Transmitters	0.5	1	2	100000	150000	1100000
Temperature indicators	0.5	1	2	140000	150000	3300000
Flow instrumentation	0.5	1	3	100000	125000	10000000
Electro-mechanical parts	0.5	1	3	13000	25000	1000000
Pressure vessels	0.5	1.5	6	1250000	2000000	33000000
Filters, strainers	0.5	1	3	5000000	5000000	200000000
Check valves	0.5	1	3	100000	100000	1250000
Relief valves	0.5	1	3	100000	100000	1000000
3.MF / RO						
Ball bearing	0.7	1.3	3.5	14000	40000	250000
Roller bearing	0.7	1.3	3.5	9000	50000	125000
Sleeve bearing	0.7	1	3	10000	50000	143000
Belts, drive	0.5	1.2	2.8	9000	30000	91000
Bellows, hydraulic	0.5	1.3	3	14000	50000	100000
Bolts	0.5	3	10	125000	300000	100000000
Clutches, friction	0.5	1.4	3	67000	100000	500000
Clutches, magnetic	0.8	1	1.6	100000	150000	333000
Couplings	0.8	2	6	25000	75000	333000
Couplings, gear	0.8	2.5	4	25000	75000	1250000
Cylinders, hydraulic	1	2	3.8	9000000	900000	200000000
Diaphragm, metal	0.5	3	6	50000	65000	500000
Diaphragm, rubber,	0.5	1.1	1.4	50000	60000	300000
gasket, hydraulics	0.5	1.1	1.4	700000	75000	3300000
Filter, oil	0.5	1.1	1.4	20000	25000	125000
Gears	0.5	2	6	33000	75000	500000
Impellers, pumps	0.5	2.5	6	125000	150000	1400000
Joints, mechanical	0.5	1.2	6	1400000	150000	10000000
Knife edged, fulcrum	0.5	1	6	1700000	2000000	16700000
Liner, recip. comp.cyl	0.5	1.8	3	20000	50000	300000
Nuts	0.5	1.1	1.4	14000	50000	500000
O-rings elastomeric	0.5	1.1	1.4	5000	20000	33000
Packings, recip.comp.rod	0.5	1.1	1.4	5000	20000	33000
Pins	0.5	1.4	5	17000	20000	170000
Pivots	0.5	1.4	5	300000	50000	1400000
Pumps, lubricators	0.5	1.1	1.4	13000	400000	125000
Seals, mechanical	0.8	1.4	4	3000	50000	50000
Shafts, cent.pumps	0.8	1.2	3	50000	25000	300000
Springs	0.5	1.1	3	14000	50000	5000000
Vibration mounts	0.5	1.1	2.2	17000	25000	200000
Wear rings, cent. Pumps	0.5	1.1	4	10000	50000	90000
Valves, recip comp.	0.5	1.4	4	3000	40000	80000
Circuit breakers	0.5	1.5	3	67000	100000	1400000
Compressors,centrifugal	0.5	1.9	3	20000	60000	120000
Compressore blades	0.5	2.5	3	400000	800000	1500000
Compressore vanes	0.5	3	4	500000	1000000	2000000

	Beta value (β) Weibull shape factor			Eta value (η) Weibull scale factor (characteristic life hours)		
Diaphragm couplings	0.5	2	4	125000	300000	600000
Motors, Ac	0.5	1.2	3	1000	100000	200000
Pumps centrifugal	0.5	1.2	3	1000	35000	125000
Transformers	0.5	1.1	3	14000	200000	14200000
Controllers, pneumatic	0.5	1.1	2	1000	25000	1000000
Controllers, solid state	0.5	0.7	1.1	20000	100000	200
Control valves	0.5	1	2	14000	100000	333
Motorised valves	0.5	1.1	3	17000	25000	1000000
Solenoid valves	0.5	1.1	3	50000	75000	1000000
Transducers	0.5	1	3	11000	20000	90000
Transmitters	0.5	1	2	100000	150000	1100000
Temperature indicators	0.5	1	2	140000	150000	3300000
Pressure indicators	0.5	1.2	3	110000	125000	3300000
Flow instrumentation	0.5	1	3	100000	125000	10000000
Level instrumentation	0.5	1	3	14000	25000	500000
Electro-mechanical parts	0.5	1	3	13000	25000	1000000
Pressure vessels	0.5	1.5	6	1250000	2000000	33000000
Filters, strainers	0.5	1	3	5000000	5000000	200000000
Check valves	0.5	1	3	100000	100000	1250000
Relief valves	0.5	1	3	100000	100000	1000000
Coolants	0.5	1.1	2	11000	15000	33000
lubricants	0.5	1.1	3	11000	15000	40000
Lube oils, mineral	0.5	1.1	3	3000	10000	25000
Lube oils, synthetic	0.5	1.1	3	33000	50000	250000
greases	0.5	1.1	3	7000	10000	33000
4. H_2O_2 addition						
Cylinders, hydraulic	1	2	3.8	9000000	900000	200000000
Diaphragm, rubber,	0.5	1.1	1.4	50000	60000	300000
gasket, hydraulics	0.5	1.1	1.4	700000	75000	3300000
Valves, recip comp.	0.5	1.4	4	3000	40000	80000
Diaphragm couplings	0.5	2	4	125000	300000	600000
Motors, Ac	0.5	1.2	3	1000	100000	200000
Transmitters	0.5	1	2	100000	150000	1100000
Flow instrumentation	0.5	1	3	100000	125000	10000000
Electro-mechanical parts	0.5	1	3	13000	25000	1000000
5. UV-irradiation						
Sleeve bearing	0.7	1	3	10000	50000	143000
O-rings elastomeric	0.5	1.1	1.4	5000	20000	33000
Controllers, pneumatic	0.5	1.1	2	1000	25000	1000000
Control valves	0.5	1	2	14000	100000	333
Transmitters	0.5	1	2	100000	150000	1100000
Temperature indicators	0.5	1	2	140000	150000	3300000
Flow instrumentation	0.5	1	3	100000	125000	10000000
Pressure vessels	0.5	1.5	6	1250000	2000000	33000000
Check valves	0.5	1	3	100000	100000	1250000
Relief valves	0.5	1	3	100000	100000	1000000

Reliability: Reliability of the machinery is derived through parametric models to serve as population models for failure times arising from a wide range of products and failure mechanisms. Weibull is a life distribution model, has been successfully useful in many applications as purely empirical model. The 2-parameter Weibull distribution function used in reliability engineering is given by:

$$f(t)=\frac{\beta}{\eta}\times\left[\frac{t}{\eta}\right]^{\beta-1}\times e^{-\left(\frac{t}{\eta}\right)^{\beta}} \qquad t\geq 0,\beta>0,\eta>0$$

and the reliability function R(t) is given by,

$$R(t)=\int_{t}^{\infty} f(x)dx=\exp[-(t/\eta)^{\beta}] \quad t\geq 0,\beta>0,\eta>0$$

Where β the shape parameter is η is the scale parameter ($1/\eta$ is the characteristic life, it is the value for which the 63rd percentile of the failure distribution is reached) and t is the time of operation. The scale parameter η has the same unit as t and the shape parameter β is the dimensionless quantity.

When $\beta=1$, represents the constants failure rate and the reliability model is converted to,

$R(t)=\exp(-\lambda.t)$ $t\geq 0$, with the failure rate, $\lambda(t)=\frac{1}{\eta}=\frac{1}{MTBF}$

Where, λ is the failure rate – 1/MTBF, the mean time between failures. MTBF is for assessed for the repairable failures, and it is expressed as MTTF for the non-repairable failures.

Maintainability: In maintainability, the random variable is time-to-repair, in the same manner as time-to-failure is the random variable in reliability. Consider the maintainability equation for a system in which the repair times follows the weibull distribution, its maintainability M (t) is given by:

$$M(t)=1-\exp[-t/\eta]^{\beta}$$

where, MTTR is given by,

$$MTTR=\eta\times\Gamma\left[\frac{1}{\beta}+1\right]$$

To calculate the maintainability or Mean Time to Repair (MTTR) of an item, the time required to perform each anticipated repair task is multiplied by the relative frequency with which that task is performed (e.g. number of times per year).

At the system level, MTTR for a total system is calculated by summing the product of the MTTR's of the replaceable items and their corresponding failure rates; the result is then divided into the sum of all replaceable items' failure rates.

MTTR (maintainability) prediction technique is a fast, simple, accurate and effective approach for providing a design baseline for repair times. MTTR prediction spots the areas of the system that exhibit poor maintainability so as to justify the improvement and modification. MTTR also helps in checking the adequacy and consistency between the systems predicted downtime logistic requirements and the system operational requirements and allocations. This kind of maintainability prediction analyses how long repairs and maintenance tasks will take in the event of a system failure, the availability of a system.

Operational availability (A_o) is the probability that an item is in an operable state at any time, and is based on a combination of MTBF (function of reliability) and MTTR (function of availability).

$$A_o = \frac{MTBF}{MTBF + MTTR}$$

Process reliability for an indirect potable recycling scheme may be engineered through reliability assessments made using Weibull distribution databases for each of the stages that employs mechanical equipment. Historical MTTR for each component should be tracked and updated through corrective maintenance work orders. The MTBF and MTTR values analysed should be a part of the asset replacement strategy.

Failure events can be defined in terms of both failure to meet treatment quality objectives and failure to meet treatment capacity objectives.

For example, if a chlorine dosing plant in the disinfection process fails, treatment quality objective will not be met. Similarly, if UV lamp fails in a UV disinfection reactor, the treatment system will not provide the necessary log reduction removal for viruses. However, in each case, it is possible for the plant to continue to meet the treatment capacity objective because the failure of the dosing pump or UV lamp does not impact the hydraulic capacity of the process.

However, if a mechanical device such as a backwash valve, pump, bearing or other component on the treatment plant fails, it may not be possible to continue to produce water because plant production is dependent particularly with membrane system, or the pressure driving force which moves water through the process.

This is an important distinction between conventional treatment process that are driven by gravity, such as drinking water treatment plants and AWT process that rely on feed pump. The former are more likely to experience failure that could impact quality but not the capacity while the later are more likely to experience failure that affects capacity.

3.5 DISCUSSION

It is widely acknowledged that it will never be possible to identify and quantify the complete mix of chemical contaminants present in a wastewater or water supply source. However, a valuable approach is to establish quantifiable limits for a series of surrogate or composite parameters (eg. TOC, fluorescence, UV absorbance, colour, etc), that would provide some information on the concentration or identity of suspected specific chemicals of concern (NRC, 1998).

A similar, but distinct approach is the use of a short specific indicator chemicals list to indicate the effective (or otherwise) performance of unit treatment processes. A framework for implementing such as approach is proposed in a separate submission to the NEPC (Drewes, 2007). A range of indicator chemicals including specific pharmaceuticals, pesticides, hormones, musks, flame retardants and disinfection byproducts are proposed primarily for monitoring the performance of reverse osmosis treatment and advanced oxidation. The chemicals are grouped into 'bins' of those for which variable removal ('good', 'intermediate', or 'poor') would be expected for a well operating system. Observed aberrations from this expected behaviour is then a useful indicator of treatment under-performance and thus of the likely reduced removal of a much wider range of chemical contaminants.

In most Australian schemes, recycled water quality is continuously monitored by 'Supervisory Control and Data Acquisition' (SCADA) systems with sensors placed at strategic locations within the treatment process and at the final point of dispatch from the plant. Typical online parameters

include conductivity, turbidity, total organic carbon (TOC) and pH. These may be used to indicate the quality of water leaving the plant as well as for closer monitoring of individual treatment modules or 'sections' of plants to identify maintenance requirements.

In some situations, monitoring membrane integrity via small ionic species (by conductivity) may be optimal since these may be expected to leak before larger species do. However, this will not always be the situation where loss of membrane integrity or short-circuiting occurs on a larger scale than the molecular-size difference between small ions and larger organic chemicals. Furthermore, many modern membranes retain ionised species considerably more effectively than they retain some comparatively larger neutral chemicals (Bellona et al., 2004). In such cases, monitoring methods targeting these larger neutral species could offer significantly more sensitive measurements. It is anticipated that fluorescence analysis may provide significantly greater sensitivity, as well as enhanced characterisation of the nature of any chemical contaminant, compared to TOC (Khan et al., 2006).

SECTION 4 Monitoring

4.1 Background

Continuous monitoring is a key aspect to ensure the quality and safety of recycled water and confirm that water quality is specified required criteria. Most of the techniques available to monitor recycled water quality are similar to those used to monitor drinking water quality, and include chemical analytical methods as well as bioanalytical toxicity testing and online monitoring methods (discussed in more detail below). Chemical analysis and *in vitro* testing are used to determine exposure, while *in vivo* bioassays are used to determine effects. One often overlooked monitoring program issue is the importance of the sampling and extraction method. A flawed or inappropriate sampling or extraction procedure will result in inadequate quantification no matter how advanced and accurate the analysis method. Therefore an equal emphasis must be placed on selection of the appropriate sampling, extraction, and analytical methods.

4.2 Sampling and extraction methods

By far the most common sampling method is grab sampling. In grab sampling, a sample of the water to be analysed is taken by filling a collection bottle. A significant limitation of this technique is the lack of time integration. All measurements on that sample will determine the water quality at that particular moment, which does not necessarily reflect overall water quality. The chemical composition of secondary treated sewage effluent (the most likely source of recycled water) can be quite variable, and it may be difficult to obtain a representative sample from one grab sample. Rather, repeated grab samples have to be taken to provide a more accurate measure of overall water quality and estimate temporal and seasonal variation, which can be time-consuming and costly as each sample needs to be analysed.

An alternative to grab sampling is composite sampling. In composite sampling, a small sample of water is taken at regular intervals and the final sample is a composite of all of these sub-samples. While this technique allows some integration for the variation in chemical contaminant concentrations over time, its most significant limitation is the fact that biodegradation can occur between the sampling times to achieve a composite sample, and the time of testing. Therefore chemical contaminant concentrations may be underestimated. It also requires the installation of electrical equipment to facilitate this type of sampling regime (such as fridges and automatic composite samplers at the sampling site), which is not always possible.

A promising alternative to grab and composite samples is passive dosimetry (or passive sampling; Namiesnik et al. 2005; Stuer-Lauridsen 2005). In passive dosimetry, passive accumulation devices (also known as passive samplers) are submerged in the monitored water and accumulate chemical contaminants by absorption or adsorption in a trap, usually a membrane. Several types of passive samplers exist, from semi-permeable membrane devices (SPMDs) that accumulate lipophilic contaminants to more polar samplers (called Polar Chemical Integrative Samplers, or POCIS) for more hydrophilic contaminants (Stuer-Lauridsen 2005). The sampling devices can be submerged in the water for several days/weeks and the concentration of chemical contaminants in the trap is integrated over the whole exposure time. This provides a long-term overview of the contaminant level. While passive dosimetry has many advantages including simplicity, low cost and the ability to determine time-weighed average contaminant concentrations, there are still significant limitations to overcome (such as impacts of environmental conditions on rates of uptake of contaminants that may hinder accurate quantification) before passive samplers can gain greater acceptance as reliable sampling tools (Namiesnik et al. 2005).

Thus, while there are alternatives, grab sampling remains the most widely-used sampling method because of its simplicity and robustness.

After sampling, an extraction technique is used to extract the targeted chemical pollutants from the sample for analysis. Metal pollutants in grab and composite water samples can be extracted using ion-selective resins (NRC 1998; Prabhakaran and Subramanian 2003), while organic chemical pollutants can be extracted using solid-phase extraction (Hennion 1999). In the case of passive samplers, the device is brought back to the laboratory at the end of the deployment period, and the accumulated pollutants are extracted (Namiesnik et al. 2005). The membrane in the device traps specific contaminants based on their chemistry, for example a C18 membrane would trap organic chemical contaminants. The extracts can then be analysed using standard chemical methods or toxicity testing.

4.3 Chemical analysis

There are many analytical techniques to measure chemical contaminants in water. Organic contaminants such as pesticides, pharmaceuticals and industrial solvents are usually analysed by combining gas or liquid chromatography (GC or LC, respectively) followed mass spectrometry (MS) (NRC 1998). Inorganic chemical contaminants such as heavy metals or chlorine can be analysed by ion chromatography (IC) (Jackson and Chassaniol 2002) or elemental analysis such as inductively coupled plasma mass spectrometry (ICP-MS) (Rosborg et al. 2006).

Chemical analysis however presents considerable limitations, most of which are due to the very large number of chemicals with biological activity that may be present in the water and the ultra-low concentrations that have been reported in the literature that are able to elicit a biological response. This means that a comprehensive analytical monitoring program must be able to measure many target analytes in ranges close to, or below, method detection limits. Also, because chemical analysis relies on separation and identification of pollutants based on their chemical structure, methods needs to be constantly updated to monitor 'emerging' contaminants. Furthermore, chemical analysis can only determine the concentration of particular chemicals in the sample, and not their potential biological potency or determine any potential complex interactions (such as synergistic or antagonistic effects) between different chemicals that may be present in the mixture. The most critical limitation of chemical methods however is their inability to detect unexpected contaminants as only intentionally selected chemicals are usually targeted to be measured. Should an unexpected chemical be present, it may not be detected if it is not sought after. In other words, chemical analysis relies on *a priori* knowledge (or assumptions) of water quality and its composition, and attempting to confirm the safety of recycled water by analysing only for known chemical contaminants (such as those in drinking water guidelines) would not provide adequate protection of human health (NRC 1998). Toxicity testing is therefore an essential component of recycled water quality monitoring.

4.4 Toxicity testing

Toxicity testing is a part of a tiered process to evaluate the risks associated with potential contaminants in water. There are three stages:

1) Chemical screening and identification study (section 4.3)
2) *In vitro* screening to determine toxic potential (section 4.4.1)
3) Integrated toxicity (*in vivo*) testing using whole animals (section 4.4.2)

Within a risk assessment framework, the first stage (chemical screening) is a measure of exposure; the second stage (*in vitro* screening) is also a measure of exposure but also incorporates aspects of effect to make the measure more toxicologically relevant; and the third stage (*in vivo* testing) is a measure of effect.

In stages 2 and 3 of toxicity testing, chemical pollutants in the water sample (some of which may have been identified in stage 1) are extracted and concentrated and challenge tests are performed with cells (*in vitro* testing) and/or whole animals (*in vivo* testing). A range of acute and chronic toxicity outcomes can be measured. In monitoring the quality of recycled water, the most relevant toxicity outcomes should be selected based on intended and potential uses of the water. In the case of recycled water for augmentation of drinking water for example, the following toxicity outcomes might be most relevant (adapted from NRC 1998):

- Acute toxicity:
    - Cytotoxic = causing cell death, which leads to acute toxicity
    - Mitogenic = affecting cell division, which can lead to acute toxicity
- Organ-specific toxicity:
    - Hepatotoxic = harmful to the liver, which can lead to an increase in liver diseases
    - Nephrotoxic = harmful to the kidneys, which can lead to an increase of kidney diseases
- System-specific toxicity:
    - Immunotoxic = harmful to the immune system, which can lead to an increase in immune diseases
    - Neurotoxic = harmful to the nervous system
    - Endocrine disruption = capable of interfering with the endocrine system and hormone signalling, which may potentially affect sperm count and hormone-related cancers
- Carcinogenicity:
    - Mutagenic = inducing DNA mutations, which can lead to cancer
    - Clastogenic = inducing chromosomal damage, which can lead to cancer
    - Genotoxic = causing harm by damaging DNA, which can lead to cancer
- Developmental effects:
    - Embryotoxic = harmful to the embryo (up to 8 weeks post-fertilization)
    - Fetotoxic = causing damage to the fetus (more than 8 weeks post-fertilization)
    - Teratogenic = causing birth defects and malformations

Unlike chemical analysis methods, toxicity tests detect chemical pollutants based on their effects in biological systems (molecules, cells or whole animals). This means that *a priori* knowledge of the chemical nature of the sample is not required. Toxicity testing also provides considerably more biologically relevant information such as bioavailability and a measure of whole mixture toxicity. The results of bioanalytical toxicity tests can then used to perform a targeted chemical analysis based on which toxicities were detected. This is discussed in section 4.6 below. It should be noted that data generated in bioanalytical techniques are generally more variable than standard analytical techniques, since biological systems are usually variable.

4.4.1 *In vitro* toxicity testing

In vitro (literally 'in-glass') toxicity tests are tests performed at the molecular or cellular level in the laboratory. Examples of molecular endpoints include binding to specific biological receptors or induction of particular signal transduction pathways, while cellular endpoints could be cell death, maturation or growth. *In vitro* tests can detect biological effects at very low environmentally relevant concentrations, often below detection limits of chemical analysis and *in vivo* testing methods (Asano and Cotruvo 2004). *In vitro* assays can be based on human cells, thus eliminating the inter-species predicament of *in vivo* testing (Barratt et al. 1995). There are

however limitations to *in vitro* bioassays that should be clearly understood when interpreting *in vitro* bioassay results, mainly that a) *in vitro* bioassays lack metabolism and transport mechanisms that may modulate toxicity in whole organisms, and b) *in vitro* bioassays detect chemical contaminants based on their "toxic" effect, but do not identify the causative chemical(s). *In vitro* assays were developed for screening purposes and there is still much debate about their ability to predict whole organism effects (NRC 1998), therefore *in vitro* bioassays should not be used as a measure of effect. However, *in vitro* bioassays are well suited to monitoring water quality (exposure assessment), as they are significantly faster and cheaper than *in vivo* exposures, are amenable to high throughput screening, and allow the generation of relatively rapid toxicology data without the need for ethically and financially expensive whole-animal experimentation (Balls et al. 1995). In recent years, there has been a move towards standardising the various *in vitro* techniques available, with the creation of European Centre for the Validation of Alternative Methods (ECVAM) in 1991 and the US National Toxicology Program Interagency Centre for the Evaluation of Alternative Toxicological Methods (NICEATM) in 1998. These two programs have generated thoroughly validated alternative methods using *in vitro* toxicity tests for some toxic endpoints.

In vitro toxicity tests exist for a variety of toxic endpoint including acute, organ specific and system-specific toxicity, as well as carcinogenicity and endocrine disruption. Estimating developmental toxicity *in vitro* is more challenging, however some *in vitro* models based on embryonic stem cells do exist (Spielmann et al. 2006) and it is likely that similar models using non-embryonic stem cells can be developed.

Several studies have used *in vitro* toxicity testing to measure chemical pollutants in Australian wastewater (Leusch et al. 2006a; Muller et al. 2007) and a similar approach could be used to monitor recycled water quality, particularly as a screen and prioritisation tool for subsequent chemical analysis (as described below and in Figure 4-1).

4.4.2 *In vivo* exposures

In *in vivo* exposures, whole animals are exposed to pollutants extracted and concentrated from the water sample, either via skin exposures or consumption (depending on the toxic endpoint considered). Whole animal toxicity testing is generally conducted using rodents such as mice or rats for a number of practical reasons. In recent years, the usefulness of *in vivo* testing with laboratory animals has been questioned. Aside from the obvious ethical cost associated with routine *in vivo* testing, there are also issues of interspecies variability which may result in a chemical being toxic in one species but not another. A classic example of this is the breast cancer drug tamoxifen, which causes liver cancer in rats but not in mice, although they are closely related species (Martin et al. 1997). This has led to concerns about the reliability of extrapolating data generated in laboratory animals to human health outcomes. In other words, the occurrence of adverse effects in any one species does not necessarily indicate such effects will occur in humans. Conservative risk assessment however dictates that adverse findings in animal species should be assumed to represent potential effects in humans, unless there is convincing evidence of species specificity. Another issue with *in vivo* studies is that doses often have to be significantly higher than environmentally relevant doses to detect toxic effects within a realistic experimental time frame (Asano and Cotruvo 2004). For example, mice and rats would be exposed to highly concentrated (500-1000x) recycled water. While the use of high doses increases the likelihood that potentially significant toxic effects will be identified, most toxic effects have a threshold level below which no adverse effects are observed, called the 'no observable adverse effects level' (NOAEL). It is therefore unclear if toxicities at such high levels of exposure would be representative of effects at normal (1x) exposure concentrations (Asano and Cotruvo 2004). An alternative to using rodents for water quality monitoring is to use fish. This presents several advantages over rodent testing: fish can be exposed to the monitored water continuously, and are

significantly cheaper to maintain in large numbers compared to rodents (NRC 1998). There are however significant biological differences between fish and humans that limit the predictive powers of such tests, and certain mammalian functions are absent in fish, and certain functions in fish are not present in mammals; the sensitivity of gills may results in overestimation of acute toxicity; and there are potentially important differences in pharmacokinetics and metabolism of chemicals in fish compared to mammals (NRC 1998). Nevertheless, some projects use online monitoring with fish tanks to measure a range of toxic endpoints in constantly exposed fish as indicators of potential human health risks associated with recycled water (WERF 2007).

In vivo toxicity testing has already been deployed in testing quality of recycled water overseas. *In vivo* exposures using rats and mice were conducted during the establishment of the Denver Potable Reuse Demonstration Project and the Tampa Water Resource Recovery Project in the USA (NRC 1998). In Denver, rats and mice were exposed to up to 500x concentrated recycled water in 2-year chronic *in vivo* carcinogenicity and reproductive/teratogenic studies. No treatment related effects were observed (NRC 1998). In Tampa, mice and rats were exposed to 1000x concentrated recycled water and multiple toxic endpoints were measured (including skin irritation, lung adenoma, 90 day subchronic, developmental and reproductive toxicity). All tests were negative, except for some fetal toxicity exhibited in rats, but not mice, exposed to recycled water (NRC 1998). The Health Effects Testing Program (HETP) conducted to test recycled water from the NEWater facility in Singapore involved *in vivo* testing with mice and fish (Expert Panel 2002). There were no differences in survival, carcinogenicity in mice and estrogenicity in fish between any of the treatments (Y. Tan, Public Utilities Board, Singapore, personal communication).

The most significant limitation of *in vivo* exposures to monitoring recycled water quality is the time required to generate toxicity data, which can vary from several months to years. This means that *in vivo* testing cannot be used to provide the project operators with rapid feedback in the event of unanticipated changes in water quality. *In vitro* toxicity testing, however, can provide a measure of toxicity within a couple of days or hours.

4.4.3 Epidemiological studies

Human epidemiological studies may be necessary to monitor human health effects during the establishment phase of recycled water for augmentation of drinking water supplies, but it is unclear what exact role they would play in monitoring recycled water quality. Designing epidemiological studies to detect the impact of drinking water on humans health has proved challenging (NRC 1998). A large population study group is required to accurately quantify whether a true difference exists between exposed and unexposed subjects, and many other environmental factors may contribute to differences between these two cohorts. The feasibility and limitations of epidemiological studies for monitoring health outcomes associated with use of recycled water is described in more details in section 5.

4.5 Online monitoring methods

Online monitoring methods (or biosensors) are an attempt to provide project operators with a very rapid bioanalytical method for water quality assessment. Biosensors integrate elements of bioanalytical and chemical methods, consisting of a biological recognition element interfaced with a chemical sensor to measure concentration of targeted chemical species (Rogers 2006). These can be (1) enzyme based biosensors that can measure interference of chemicals in the water with enzyme activity; (2) antibody based biosensors that bind groups of structurally-related compounds with a wide range of affinities; (3) receptor-based biosensors that can be used to screen for a wide range of structurally diverse pollutants that can bind to specific biological receptors; (4) DNA-based biosensors that can detect DNA damage potentially induced by the mixture of chemicals present in the water sample; and finally (5) more complex cell-based biosensors that can change in whole cells in response to chemicals present in the water sample (Rogers 2006). Biosensors show tremendous potential for development as online biological early warning systems (BEWS), but still require significant research to achieve acceptable levels of durability, selectivity/specificity, extended concentration ranges (sensitivity), and resistance to biofouling before they receive widespread acceptance in this field (Rogers 2006).

4.6 Proposed framework for combined bioassay and chemical analysis

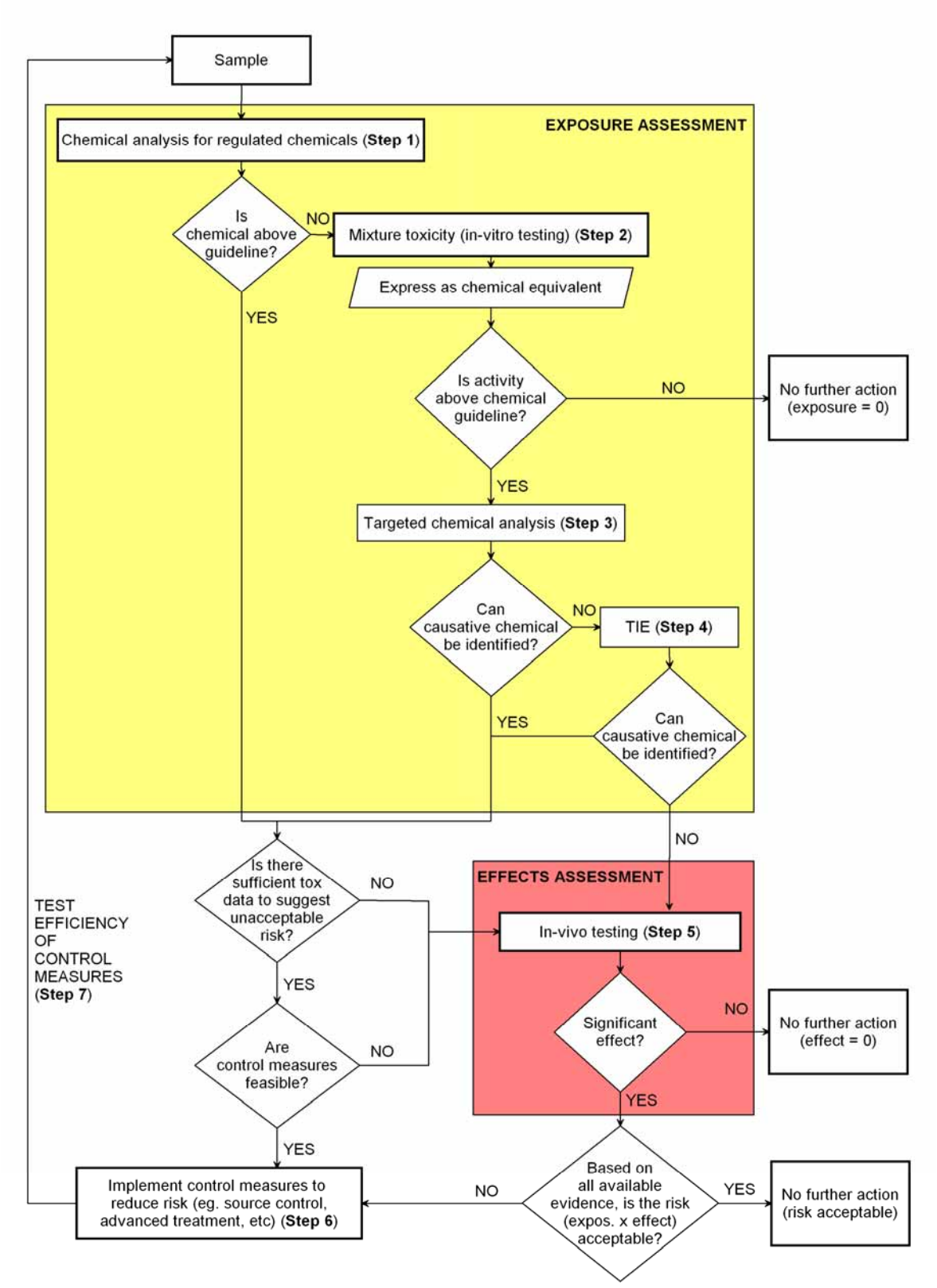
As previously stated, bioanalytical toxicity testing measures total biological activity in a given water sample, but does not provide identification of the causative chemicals. Chemical analysis on the other hand only allows measurement of selected chemicals, and biologically active compounds may be missed because they were not originally targeted. But combining the two techniques provides significantly more analytical power than each individual method alone. In this approach, water samples are first tested using conventional chemical analysis targeting individual chemicals with a guideline (this document and the Australian Drinking Water Guidelines) (Step 1, Figure 4-1). If none of the measured chemicals are above their respective guideline values, then *in vitro* bioassays are used to screen the samples for biologically-active compounds as well as provide a limited measure of mixture toxicity (Step 2, Figure 4-1). The responses in the bioassays are expressed as a "chemical equivalent" for which a guideline value exists (for example, an estrogenic response could be expressed as "17β-estradiol equivalent", a chemical with a guideline of 0.175 µg/L in this document). If the response in the bioassay exceeds the guideline value, then the sample is forwarded for targeted chemical analysis based on the type of toxicity measured and the most likely candidate chemicals (Step 3, Figure 4-1). For example, if a significant estrogenic effect was measured in toxicity tests (ie. the 17β-estradiol equivalent of the sample as determined by *in vitro* bioassay exceeds the guideline value of 0.175 µg/L), a targeted chemical analysis of known estrogenic chemicals (such as natural and synthetic hormones, nonylphenol and bisphenol A) would be carried out.

If the causative chemicals cannot be identified through a targeted chemical analysis, then a full toxicity identification evaluation (TIE) may be necessary (Step 4, Figure 4-1). In a TIE protocol, samples are fractionated both physically and chemically and each fraction is then re-tested in bioassays to assess which manipulation removed or mitigated the toxicity of the sample. This helps identify the class of the causative chemical. For example, volatile organic compounds would be suspected if aeration of the sample significantly reduces toxicity. The toxic fraction is then further fractionated using more advanced separation techniques such as high performance liquid chromatography (HPLC) and again tested in biological and chemical assays to identify the exact nature of the chemical. Once identified, a confirmation step is usually performed to ensure that the causative pollutant has been correctly identified by testing the activity of the chemical

compound in the bioassay. If after a TIE the causative chemical can still not be identified, then a full effects assessment may be required (Step 5, Figure 4-1).

Once the chemical has been identified (at Steps 1, 3 or 4; Figure 4-1) or the effects assessment has been conducted (Step 5, Figure 4-1), then an informed decision can be made on the need for further risk mitigation and the implementation of control measures (Step 6, Figure 4-1). Of course, the efficiency of those control measures then needs to be tested using the full framework (Step 7, Figure 4-1).

Figure 4-1: Proposed framework for toxicity testing for mixtures and unknown or unexpected chemicals.



4.7 Surrogates and indicators

A framework for monitoring surrogate parameters (eg. TOC, fluorescence, UV absorbance, colour, etc) and indicator chemicals is proposed in a separate submission to the NEPC (Drewes, 2007). This framework is endorsed by the authors of the current document, however it is considered unnecessary to reproduce the details here. In short, the framework involves the use of surrogate parameters and indicator chemicals for monitoring the effective performance of key advanced water treatment operations. A range of indicator chemicals including specific pharmaceuticals, pesticides, hormones, musks, flame retardants and disinfection byproducts are proposed primarily for monitoring the performance of reverse osmosis treatment and advanced oxidation. The chemicals are grouped into "bins" of those for which variable removal ("good", "intermediate", or "poor") would be expected for a well operating system. Observed aberrations from this expected behaviour is then a useful indicator of treatment under performance and thus of the likely reduced removal of a much wider range of chemical contaminants.

4.8 Summary

There are several methods to monitor the chemical quality of recycled water. These methods fit into a tiered toxicity testing framework to determine risks associated with pollutants in recycled water (Figure 4-1). Great care must be given to the selection of sampling, extraction and analytical methods. At the moment, the preferred approach is to screen multiple grab or composite samples using *in vitro* toxicity testing, and to forward positive samples for targeted chemical analysis to determine causative chemicals. New technologies such as passive dosimetry and online biosensors show high potential but need to be researched and established further before they can become reliable tools.

SECTION 5 Exposure and public health surveillance

5.1 Introduction

The intent of the Australian Drinking Water Guidelines and drinking water treatment chemicals guidelines is to ensure that at the point of consumption, water supplies meet rigorous standards which have been promulgated to ensure public safety. Water suppliers have generally adopted the HACCP (or similar risk management) principles in the management of the engineering process of water treatment. The background to this is well described in the CRCWQT document on 'Hazard Identification and Risk Assessment for Drinking Water Supplies'. In these circumstances public health surveillance is unlikely to be necessary other than where a breakthrough has taken place or where there is evidence of community illness that might be associated with waterborne exposure to chemicals of interest.

5.2 Public health surveillance

Public health surveillance has traditionally aimed at providing early warning of possible health problems associated with microbiological water safety. Such surveillance provides an oversight on all aspects of the presence and spread of disease necessary for effective control of the microbiological safety of water. This form of surveillance demands the systematic collection and evaluation of data relating to:

- morbidity and mortality;
- investigation of epidemics and individual instances of disease;
- isolation and identification of infectious agents;
- availability and use of vaccines, antibiotics and other substances used in disease control;
- establishment of the levels of immunity in the population;
- relevant epidemiological information.

This form of disease surveillance in the community is quite separate from the surveillance of health in individuals. It can encompass the possible health consequences of exposure to various toxins and chemicals. It is primarily designed in part, or in whole, to meet the needs of the community that uses the water supply. Where the drinking water supply is going to be augmented with recycled water, the issue that arises is whether or not the finished water is likely to present a different health risk to unaugmented drinking water. Surveillance will be distinct from epidemiological evaluation water exposure because it is an ongoing public health process analogous to continuous monitoring. The ability of any surveillance system to foreshadow a warning of possible health problems depends upon its sensitivity and threshold of detection. Since most public health surveillance is associated with microbiological safety, such programmes are characteristically designed to establish the presence of acute or sub-acute illness and not to establish chronic effects of long-term exposure to chemicals and/or other toxins. Understanding disease of this nature is more amenable to epidemiological investigation.

Epidemiological investigations are the most reliable when carried out after an event rather than beforehand. However the "event" (exposure to a compromised water supply due to catastrophic failure of the treatment system) is unacceptable and the community would likely not consider prospective epidemiological evaluations if water supplies became compromised. In well managed processes, documented and functional controls and contingency plans are in place that would stop

or minimise population exposure to the water, based on a case-by-case risk assessment (includes hazard identification and exposure considerations). This means that there would be little or no likelihood that gross contamination of water supplies would take place and that there would be little or no likelihood of acute illness. This level of control means that any epidemiological investigation will need to identify subtle chronic and difficult-to-identify health outcomes. The reference values set out in this document have the primary purpose of forestalling such an event.

There are three possible ways in which surveillance could be pursued:

- surveillance of the presence of a hazard
- the establishment of exposure - exposure surveillance
- where effects have become established associated with these exposures - outcome surveillance.

We consider that the first of these has greatest power to prevent illness by removing any possibility of exposure. There is however a stage before hazard surveillance which involves appropriate controls on the presence of hazards using HACCP (or similar risk management) principles.

If surveillance is considered necessary it can be used to identify and trace waterborne health hazards and outcomes associated with them. However if the water recycling facility is operating within its design parameters, meets Australian Drinking Water Guidelines risk management principles, and considers the guidelines developed as part of this paper, it would seem unlikely that surveillance beyond that already established as part of the normal process of water monitoring would be necessary.

As indicated above, public health surveillance structures are already in place in most communities receiving reticulated drinking water supplies. Most jurisdictions have mandatory reporting systems which require medical reports of disease to the appropriate state or federal health departments. The purpose of surveillance systems is to prevent or control the occurrence of adverse health outcomes associated with drinking water. Critical to any such programme is the recognition that multiple agencies are involved in the production and distribution of drinking water and that management of health is usually the remit of another agency. It is clear that any ongoing surveillance programme requires close coordination and communication between these agencies including the development of emergency response plans.

5.3 Exposure to chemical contaminants from sources other than water

Drinking water is only one vector by which human exposure to harmful chemical materials can occur. Indeed, drinking water quality in Australia is guided by the Australian Drinking Water Guidelines (ADWG), and assists in the assurance that appropriately managed drinking water sources are unlikely to contribute to the exposure of such chemicals. It is much more likely that food consumption, or exposure to contaminated airsheds, represent the principal chemical exposure vectors to humans.

Food exposure is the most likely exposure vector for a range of ingested chemical contaminants. There is a substantial literature on the presence of toxic metals, pesticides and even radiochemicals as anthropogenically derived food contaminants, quite apart from the presence of natural toxins such as those produced by fungi and plants.

Airborne contamination represents an unavoidable source of chemical exposure as part of modern day living in urban environments. However many of these chemicals are not associated with water. This is largely because many are either gases, or insoluble such as particulate matter persistent organic chemical pollutants.

It can thus be seen that the subset of chemical contamination likely to be associated with water is relatively minor compared to the potential exposures associated with these other two vectors.

Box 5-1. Estimated daily exposure to N-nitrosodimethylamine (NDMA).

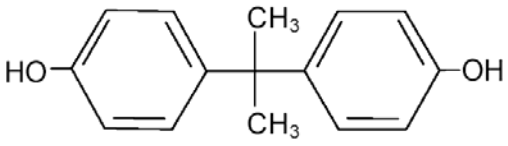
Reaction of disinfectants (such as chlorine or chloramine) with natural organic matter (NOM) in water can generate a variety of disinfection byproducts, including NDMA (N-Nitrosodimethylamine). NDMA is classified as a probable human carcinogen (NTP 2005) and its occurrence in recycled water used for augmenting drinking water supplies therefore raises human health concerns. However the concentrations of NDMA present in recycled water need to be kept in perspective with concentrations from other sources, particularly dietary sources:

- Concentrations of NDMA in Australian food is unknown, but dietary intake of NDMA in North America has been estimated at 0.1 – 0.11 µg/d from foods such as fish, dairy products including infant formula, meat, cereals, vegetables and beer (Fristachi and Rice 2007). Moreover cooking can significantly increase the formation of NDMA in food (Lee et al 2003), and the daily dietary intake of NDMA in Australia is likely to be higher than 0.1 µg/d.
- The most significant source of NDMA appears to be from endogenous formation from secondary amines such as DMA (dimethylamine) contained in ingested fish or meat. Stomach acid reacts with nitrate/nitrite from vegetables to form nitroso groups, which are then free to react with amines to form NDMA (Fristachi and Rice 2007). Endogenous formation of NDMA was estimated at 9.9 µg/d for children and 22.9 µg/d for adults based on a North American diet (Fristachi and Rice 2007).
- NDMA has also been detected in inhalable cigarette smoke (Tricker and Preussman 1992).

The total daily intake for NDMA including both exogenous and endogenous sources was estimated at 10.1 to 23.1 µg/d for children and adults, respectively (Fristachi and Rice 2007).

Based on the recycled water guideline of 0.01 µg/L proposed in this document, the estimated daily NDMA intake per day from consumption of 2 L of recycled water would be a maximum of 0.02 µg/d, i.e. less than 0.2% of the total estimated daily exposure.

5.3.1 Case study 1 Bisphenol A



Structure of Bisphenol A

Bisphenol A (BPA) is the common name for 2, 2-(4, 4-dihydroxydiphenyl) propane. BPA may be present in recycled water as a result of direct or indirect releases from manufacturing or processing facilities, or release of unreacted monomer from manufactured products (EFSA 2006, CERHR 2007). BPA is in some food contact materials because it is used in the production of polycarbonate plastic and epoxy-phenolic resins. Polycarbonate plastic is widely used in articles such as food containers (e.g., milk, water, and infant bottles), tableware (plates, mugs, jugs, beakers), microwave ovenware, storage containers, refillable office water containers and medical devices. Polycarbonate is also used for water pipes, as structural material in a wide variety of consumer goods and automotive parts, and in coatings, adhesives and fillers. Epoxy-phenolic resins are used for internal protective linings in food and beverage cans, and as a coating on metal lids for glass jars and bottles. Epoxy-phenolic resins are also used as a surface-coating on residential drinking water storage tanks and wine vats.

5.3.1.1 Background

The primary reason for choosing BPA as a case study providing a detailed analysis of the influence of the recommended drinking water guidelines on human health is the controversy surrounding potential effects of ultra low doses of BPA on reproductive health. This concern has primarily stemmed from test tube and short term hazard screening studies in rodents that show BPA possesses estrogen hormone mimicking potential. However, the estrogenic potency of BPA relative to that of estradiol has been shown to be weak (EFSA 2006, CERHR 2007).

Combinations of *in vitro* and *in vivo* screening tests are now being applied to identify chemicals which may interact with estrogen receptors (ER). Chemicals positive in the screening assays are then meant to be subject to longer term *in vivo* tests that can be used for human risk assessment purposes. The *in vitro* assays include various ER binding assays, ER transcriptional activation assays which measure an effect arising from ER activated DNA transcription in yeast or cultured mammalian cells, and cell proliferation assays using cultured human breast cancer cell lines (e.g. MCF-7 or ZR-75-1 cells) which are estrogen responsive. The *in vivo* screening test used for identifying potential estrogenic effects is the rodent uterotrophic assay. This test has many protocol variations; the chemical can be administered orally, subcutaneously or intraperitoneally to either immature, ovarectomised or hypophysectomised rats or mice and the change in uterine weight, epithelial cornification or capillary permeability measured. The latter are parameters that increase in response to activation of the ER in the uterus.

Data from these assays should not be over interpreted. For example the ability of a chemical to bind or activate rat uterine ER in the test tube should not be used to infer that an effect in rodents or humans is imminent after exposure. Similarly positive results in the uterotrophic assay using subcutaneously or intraperitoneally administered doses do not necessarily indicate effects will occur in rodents, or humans, exposed orally to environmentally relevant concentrations. Positive results from *in vitro* tests or the uterotrophic assay are merely indicative of a potential to interact with certain parts of the endocrine system under very specific and artificial conditions. They are not necessarily predictive of either animal or human adverse effects when the intact animal is exposed in a relevant manner.

Nevertheless there is general agreement that high doses of chemicals with hormonal activities may have effects on human reproduction and may cause reproductive toxicity (Witorsch 2002). However the issue of possible effects due to exposure to low doses of chemicals that have weak endocrine activities in sensitive species of rodents, and the implications of these possible effects for human health risk assessment, is emotive and vigorously debated. BPA is illustrative of the issues and the type of data required to address such concerns. Aspects requiring consideration when evaluating low dose effects of BPA, or any other chemical, in rodents for human health risk assessment include:

- Robustness and reproducibility of low dose effects.
- Possible health significance of the changes reported after low-dose administration.
- Toxicokinetics and
- toxicodynamics of the substance.

The tests most useful for risk assessments are those in which intact animals have been administered the chemical using a relevant dose route and where observations pertinent to the endocrine system being investigated have been made. The tests include developmental assays where the chemical is given throughout the sensitive period of development and organisation of the male reproductive system and there has been a detailed evaluation of sexual organs and function in offspring. Regarded by many as being the definitive reproductive assay is the multigenerational test in which two or more generations (male and female) are continually exposed (*in utero*, during lactation, and as adults) and in which morphological evaluations of sensitive tissues as well as reproductive performance and fertility are conducted. Complicating the interpretation of results of all of these tests is the recognition that there is large variability in the sensitivity of different strains of animals and between species towards estrogens (Ashby 2001, Long et al. 2000, Spearow et al 1999). This creates difficulty in comparing results between laboratories and extrapolating results to humans.

The EFSA (2006) considers that while low-dose effects may be theoretically possible (Conolly and Lutz 2004), low dose effects of BPA in rodents have not been demonstrated with sufficient certainty to serve as pivotal studies for risk assessment. The more recent observations of species differences in toxicokinetics of BPA between primates, including humans, and rodents, and in particular the low bioavailability of BPA in primates (see below), further weaken the relevance of observations of low-dose effects of BPA in sensitive strains of rodents for human health risk assessment. Nevertheless reported low-dose effects of BPA in a number of different animal systems and on different reproductive or developmental endpoints, and the inability to reproduce these effects in larger and statistically more powerful studies has generated controversy.

Following an initial report (Nagel et al. 1997) of increased prostate weight in offspring of mice that were exposed orally to very low doses of BPA (2 and 20 µg/kg/d on gestational days 11 -18) there have been many conflicting results regarding this finding. Most of the positive results arise from a single laboratory where it is claimed an increase in prostate weight in rodents is indicative of an adverse effect that may have implications for humans (e.g. prostatitis, benign prostatic hyperplasia or cancer).

Thus Nagel et al. (1997), vom Saal et al. (1998), Howdeshell et al. (1999) and Gupta (2000) found increased prostate weight and/or other sex organ effects, including accelerated puberty, in mice exposed *in utero* to 2 - 50 µg BPA/kg/d given orally. Al-Hiyasat et al. (2002) observed decreases in testicular and epididymal sperm counts and decreased fertility in Swiss mice given 0.025 or 0.1 µg/kg/d BPA intragastrically for 30 days. None of these effects have been confirmed in larger *in utero* exposure studies in mice (Ashby et al. 1999, Cagen et al. 1999, Nagao et al. 2002 with doses from 0.2 - 200 µg/kg/d) in which a range of male reproductive organs were evaluated, nor in rats (Cagen et al. 1999 and Welsch 1999 with doses from 0.002 µg/kg/d through to 10 mg/kg bw/d).

Sakaue et al. (2001) reported that oral exposure of sexually mature male SD rats to 20 µg/kg to 200 mg/kg BPA between postnatal days (PND) 91–97 led to reduced daily sperm production 5 weeks later. However Ashby et al. (2003) could not replicate these observations in four independent studies using the same protocol with doses of 20 µg/kg, 2 mg/kg, or 200 mg/kg BPA.

Sharp et al. (1995) using doses of 100 - 350 µg/kg/d in drinking water found reduced testis size in rats. These observations have not been confirmed by Cagen et al. (1999), Welsch (1999) or Elswick et al. (2000) with doses from 0.002 µg/kg/d to 10 mg/kg bw/d, or by Tinwell et al. (2002) using doses of 20 - 50 mg/kg/d, or by Kwon et al. (2000) with doses of 3.2 – 320 mg/kg/d, or in multigenerational studies (Ema et al. 2001, doses 0.2 - 200 µg/kg/d; or Tyl et al. 2002 with doses 1 µg/kg/d through to 500 mg/kg bw/d), nor even by Sharp et al. (1998) when repeating the experiments.

Ashby and Tinwell (1998) and Ashby (2001) discuss possible reasons why there may be such vastly different results between seemingly similar experiments. On the other hand Milman et al. (2002) have evaluated the various *in utero* studies for their possible usefulness in human risk assessment. They concluded the many experimental differences between the low dose studies complicate the ability to use the results to predict potential prostate effects in humans. Nevertheless, for a variety of experimental conditions and with agents other than BPA, they found no consistent correlation between prostate size, prostate pathology, and the development of prostate cancer. They concluded that a finding of increased prostate weight in rodent studies with perinatal exposure to chemicals, in the absence of associated pathologic and/or functional changes is meaningless and not indicative of a potential adverse effect in humans.

EFSA (2006) had considerable reservations about both the biological significance of the reported observations and the robustness of the studies. They noted "the effects of BPA reported in some studies at low doses in sensitive animal systems were small changes in organ weight or changes in tissue architecture, increased or decreased receptor expression, changes in hormone concentrations in plasma or tissues, small changes in the time required to attain puberty landmarks, and behavioural effects". Furthermore EFSA considered that "the changes observed were often not sustained through adulthood. The biological consequences of many of the changes in the affected animals are unknown and some, such as small increases in prostate weight, are not considered as precursors of pathological change. While some of the changes may be indicative of biomarkers of effect in very sensitive species and strains, in the light of present knowledge, they cannot be readily interpreted as adverse effects. Furthermore it was noted that the results of the studies reporting low-dose effects are in contrast to the results of muligeneration studies using comprehensive protocols developed for testing both structure and reproductive function in parents and offspring and performed following internationally recognised guidelines with regard to study design and animal model selection". EFSA (2006) have therefore relied on the latter studies for developing safe intake levels of BPA for the general public.

5.3.1.2 Toxicity relevant to risk assessment

In primates, including humans, BPA is rapidly absorbed from the gastrointestinal tract but undergoes exhaustive first-pass metabolism to BPA-glucuronide in the gut wall and liver. BPA-glucuronide was the only metabolite of BPA detected in human urine and blood samples and ingested doses of BPA were close to 100% recovered in urine as BPA glucuronide (Volkel et al. 2002) within 24 hours after administration. The plasma half life of BPA is less than 1 hour (Kurebayashi et al. 2002). Formation of BPA glucuronide is a detoxification reaction since it has much lower hormonal activity relative to BPA (Matthews et al. 2001; Shimizu et al. 2002; Snyder et al. 2000; Stowell et al. 2006) which in turn is significantly lower than natural estrogenic hormones (see below).

The extensive first-pass biotransformation, rapid elimination and protein binding of BPA means that only low amounts of the parent BPA reach the systemic circulation in humans, even after worst case dietary exposures (EFSA 2006). There is no evidence of potential for bioaccumulation in tissues.

In contrast to primates, BPA-glucuronide formed in the liver and the intestinal wall of rats undergoes enterohepatic circulation. The glucuronide is cleaved back to BPA which is then reabsorbed (Kurebayashi et al. 2005, Sakamoto et al. 2002). The enterohepatic recirculation results in slow elimination from the body with an apparent terminal elimination half-live in rats of between 19 and 78 h (Domoradzki et al. 2004, Kurebayashi et al. 2003, Kurebayashi et al. 2005; Pottenger et al. 2000). Urinary excretion of BPA and its metabolites in rats accounts for only 10 to 40% of applied dose.

Substantially less BPA is absorbed after oral administration than when it is given subcutaneously or intraperitoneally (Pottenger et al. 2000). This has implications for the interpretation of endocrine disruption screening tests where the latter routes of administration are frequently used. In addition, the glucuronidation metabolism pathway which is responsible for first pass elimination of BPA becomes saturated with oral doses of around 200 mg/kg to rats (Degan et al. 2002). Consequently disproportionately higher blood levels and longer clearance times occur with high oral doses than with lower doses.

Since most of the toxicological studies with BPA have used rodents, the difference in kinetics between species is important when assessing BPA risks to humans. Relative to humans, rats receive a much higher systemic dose of BPA. Consequently use of an ADI based on rodent NOAELs in human risk assessments is conservative if account has not been taken of the major kinetic differences between rodents and humans. It is noted that the ADI generated by EFSA (2006), and used in this document to calculate drinking water guidelines for BPA, does not make adjustments for kinetic differences as recommended can be done by WHO (1994a) and NHMRC (1999).

BPA is not genotoxic or carcinogenic (EC 2002a, EU 2003, Haighton et al. 2002).

The results of numerous *in vitro* screening assays shows BPA has weak binding and agonist properties towards estrogen receptors (e.g. Coldham et al. 1997, Gaido et al. 1997, Leffers et al. 2001). 17β-estradiol (E2) is the natural ligand for the receptors and the activity of BPA in these assays varies from being 200 to 1,000,000 times less potent than E2, most tests indicate about a 10,000 times difference. Oral doses of BPA at 200 mg/kg/d or above were effective in eliciting an uterotrophic response in rats, but 100 mg/kg/d was ineffective (Ashby and Tinwell 1998, Laws et al. 2000). The oral no effect level in the rat uterotrophic assay is 100 mg/kg/d. In mouse uterotrophic assays subcutaneous administration has resulted in both positive and negative outcomes. The weight of evidence from screening tests is that BPA may have weak estrogenic activity which can be elicited only in the special circumstances of some screening test protocols.

Due to the potential hormonal activity of BPA, albeit weak, the toxicological effects of concern are developmental and reproductive. There are a large number of developmental and reproductive studies investing a range of endocrine, hormonal, developmental and reproductive parameters that have been published in the last few years. According to EFSA (2006) the available studies cover the majority of endpoints considered relevant for assessment of reproductive effects and other toxicities and do not indicate the presence of effects on reproduction or development at doses lower than 50 mg/kg bw/day. The pivotal multigeneration studies underpinning the TDI are described below.

Multigeneration reproductive studies
Two rat multigenerational reproductive toxicity studies have been published (Ema et al. 2001, Tyl et al. 2002) and an unpublished two-generation study in mice (Tyl et al. 2006) was available to EFSA for their deliberations. All the studies were well performed using an internationally accepted reproductive toxicity protocol and conducted under Good Laboratory Practice (GLP) regulations. They undertook very detailed evaluations of offspring which included most, if not all of the sensitive and controversial endpoints relevant for assessing estrogen modulation of reproductive organs during development and reproduction.

The investigation of Ema et al. (2001) was a low dose (0.2 - 200 µg/kg/d given by oral intubation) two-generation study in rats that also evaluated potential behavioural effects. There were no compound related effects on behaviour, no effects on a myriad of sensitive reproductive performance indices, no histological effects on reproductive organs or other tissues of either sex or generation. There were slight changes in anogenital distance with the top doses in F1 males and females, and in F2 females but these changes were within 5% of control values. The data indicate that oral doses of BPA between 0.2 and 200 µg/kg/d over 2 generations did not cause significant compound related changes in reproductive or developmental parameters in rats.

Tyl et al. (2002) conducted a 3-generation reproductive dietary toxicity study in rats with a wide dose range from the very low (1 µg/kg/d) to the very high (500 mg/kg/d) administered in the diet. Adult systemic toxicity (reduced body weights, reduced absolute but increased relative organ eights) was observed at 50 and 500 mg/kg/d in all generations. Reproductive organ histopathology and function were not affected by any dose. At the top dose of 500 mg/kg/d vaginal patency and preputial separation were delayed in F1, F2 and F3 offspring and was associated with decreased body weight. The adult systemic NOAEL was 5 mg/kg/d (based on decreased adult body weights), and the reproductive and postnatal NOAEL was 50 mg/kg/d. There were no treatment related effects in the low dose region (1 – 5 mg/kg/d). The authors concluded that BPA should not be considered as a selective reproductive toxicant. The results of Kwon et al. (2000) support the conclusions of Tyl et al (2002). Kwon et al (2000), with gavage doses of 3.2 – 320 mg/kg/d, found female pubertal development was not affected and that male reproductive organ weights were unaffected.

The second study by Tyl et al. (2006) used an estrogenic sensitive mouse strain (CD-1) and was conducted according to the current OECD 416 test guideline. Apart from the traditional evaluation endpoints others included anogenital distance measurements, estrous cyclicity, total prostrate weight plus ventral and dorsolateral lobe weights. Dietary doses were 0, 0.003, 0.03, 0.3, 5, 50, or 600 mg/kg bw/day. There were no treatment-related effects on reproductive parameters at any BPA dose. The top dose induced systemic toxicity expressed as reduced body weights and increased kidney and liver weights adults, treatment- related reductions in spleen and testes weights were observed in the F1 and F2 weanlings at this dose. There was also mild centrilobular hepatocyte hypertrophy, some nephropathy, and hypoplasia of seminiferous tubules correlating with decreased testis weight. At 50 mg/kg bw/day, the only treatment-related effect observed was an increased incidence of centrilobular hepatocyte hypertrophy of minimal to mild severity in

adults. At all the lower BPA-doses (<50 mg/kg bw/day), no treatment-related effects were observed. This study gives a clear overall NOAEL of 5 mg/kg bw/day, with liver toxicity as the most sensitive endpoint. The NOAEL for reproductive effects was 50 mg/kg bw/day. The study included a positive control group of estradiol which gave the expected results associated with estrogen exposure in this strain of mice.

In summary, there is available an extensive database on repeat dose toxicity, reproductive and developmental toxicity of BPA in rodents and on the comparison of toxicokinetics in primates, including humans, and rodents. EFSA (2006) concluded, in view of the well described species differences in toxicokinetics, showing a low level of free BPA in humans compared with rats, that a default uncertainty factor of 100 applied to the overall NOAEL from the rodent studies can be considered as conservative. A TDI of 0.05 mg BPA/kg bw was derived by applying a 100-fold uncertainty factor to the overall NOAEL of 5 mg/kg bw/day.

5.3.1.3 Exposure estimates

Exposure to BPA has been determined by:

- measurement of BPA concentrations in the exposure media (food, air water, dust) in combination of estimates of how much people eat, breath and drink, or
- measurement of urinary excretion of BPA metabolites over 24 hours. Because humans excrete 100% of the daily dose in 24 hours urinary measurements equate with the absorbed dose. Estimates of the applied dose are made from assumptions of bioavailability (usually 100%, although in some studies 50%).

Estimates of daily exposure based on urinary measurements are lower than those which have used the dietary method for approximating exposure. This is considered to be the result of conservatism embedded in the latter technique (EFSA 2006).

It is noted that dietary sources account for approximately 99% of BPA exposure (Wilson et al. 2003).

Exposure sources incorporated in dietary estimations include exposure associated with BPA migration from packaging into foods; included were fruit juices, meats, fruits, vegetables, fatty foods, dairy products and general beverages. Some of the exposure estimates encompassed exposures from use of polycarbonate tableware, containers used to store food, wine storage vats, polycarbonate infant feeding bottles, migration from PVC used for pipes, hoses or lining of steel pipes, and from epoxy-phenolic resins used as a surface-coating agent in wine vats, residential drinking water storage tanks and in water heaters in households.

ESFA (2006) have made the following conservative aggregate estimates of potential dietary exposure to BPA:

Receptor	Dietary assumptions	Total intake (µg/kg bw/d)
3 month infant	fed using a polycarbonate bottle and reconstituted formulae that may contain BPA from the packaging	11
3 month infant	fed as per 3 month infant but inclusion of BPA migrated into food from epoxy resin can lining into commercial foods	13
child (1-5 years)	fed as per 3 month infant but inclusion of BPA migrated into food from epoxy resin can lining into commercial foods	5.3
adult	60 kg, consuming 3 kg of commercial food and beverage per day	1.5

In contrast, EFSA (2006) report assessment of BPA exposure in the general population by biomonitoring urinary excretion of metabolites gives an estimated average daily total exposure to BPA of up to 7 µg/adult/day and upper range exposures up to 10 µg/adult/day (0.16 µg/kg bw/day for a 60 kg person) in the USA, and 0.04 to 0.08 µg/kg bw/day in Japan (95 % confidence interval).

CERHR (2007) describe different studies investigating the intake of BPA based on urinary measurements. For 6 – 8 year old girls in the US BPA intake ranges from <0.012 – 2.17 µg/kg bw/day (median 0.07 µg/kg bw/day). The median intake for adults is 0.026 µg/kg bw/day, with 10^{th} to 95^{th} percentile intakes of 0.005 – 0.159 µg/kg bw/day.

5.3.1.4 Influence of BPA in drinking water made from recycled water on exposure

BPA intake estimates for Australians were not located. However from the above descriptions it is conservatively assumed that exposures are ≤1 µg/kg bw/day for adults and up to 5 µg/kg bw/day for children. These assumptions for Australians are based on European estimates which use conservative migration values of BPA from packaging into food and the 95^{th} percentiles of food consumption. They are similar to those reported by Haighton et al. (2002). It is noted that urinary measurements yield BPA intakes that are around ten times lower.

At the drinking water guideline limit:
When considering the possible health impacts of chemicals in recycled water that may be used for augmenting drinking water it is important to consider a number of factors that will affect the concentration in the water delivered to the consumer. One of these is the fact that the source water will undergo treatment to ensure it meets the health guidelines recommended in this document.

The recommended guideline for BPA in drinking water is 200 µg/L. If a 70 kg adult drank 2 L/day at this concentration then the intake would be 5.7 µg/kg bw/day[14] and the total intake approximately 7 µg/kg bw/day[15]. This combined exposure estimate is well below the safe intake level of 50 µg/kg bw/day established by EFSA (2006) (see above). It is 7,000 times less than the low adverse effect level (LOAEL) of 50 mg/kg bw/d observed for the most sensitive endpoints in multigeneration reproductive toxicity tests, ie liver effects in a two generation mouse study (Tyl et al 2006) and reduced adult bodyweights in a three-generation rat study (Tyl et al. 2002).

At most likely concentrations in drinking water:
In reality BPA concentrations in drinking water augmented with recycled water will be significantly less than the recommended drinking water guideline. The unrealistic worst case situation is that the levels in the final drinking water will be the same as that in the source water. BPA has been measured in secondary effluent in Australia at concentrations up to approximately 0.04 µg/L. Even if the concentrations in drinking water were ten times this level the total intake [16] would be 1.01 µg/kg bw/d; ie 1% greater than the assumed background, ~50 times less than the ADI and ~ 50,000 times less than the LOAEL.

There are also other factors that may need to be considered, for example the EFSA (2006) noted that chlorination of drinking water rapidly oxidises BPA. Thus any low amounts of BPA that may

[14] (200 µg/L x 2 L/d) ÷ 70 kg = 5.7 µg/kg bw/day
[15] Assumed adult background exposure 1 µg/kg bw/day + 5.7 µg/kg bw/day = 6.7 µg/kg bw/day (ie ~ 7 µg/kg bw/day)
[16] 10 x 0,04 µg/l = 0.4µg/l then intake is (0.4µg/L x 2L/d) ÷ 70kg = 0.01 µg/kg bw/d from the drinking water. This added to the conservative background intake of 1 µg/kg/d for an adult gives 1.01 µg/kg/d.

emerge from recycled water treatment will be easily destroyed by subsequent disinfection of the water.

It is concluded that it is unlikely BPA will be in drinking water made from recycled water, but if small amounts of BPA in drinking water should occur they are of no health consequence.

5.3.2 Case study 2 Xenoestrogens

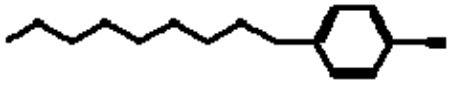
Xeno-estrogens are chemical that can mimic and/or interfere with the action of natural estrogen hormones in organisms. Estrogen hormones are involved in a variety of biological functions such as development, puberty, behavior, gametogenesis and integrated sexual function.

These environmental pollutants are ubiquitous, present not only in water but also in air, soil and food. Drinking is thus not the only source of exposure, and other pathways such as diet, cosmetics or medical applications can result in significant exposures to xeno-estrogens.

5.3.2.1 Industrial xenoestrogens

Industrial xeno-estrogens are generally not very potent xeno-estrogens (Table 5-14) but being produced in very large volumes they can be found at high concentration pollutants in water and other sources.

4-Nonylphenol



4-Nonylphenols (NPs) are a degradation product of a widely used group of nonionic surfactants, nonylphenol polyethoxylates (NPEOs). NPs have been shown to be estrogenic *in vitro* (Routledge and Sumpter 1996) and *in vivo* (Sharpe et al. 1995). NPs are ubiquitous and can be found at high concentrations in foodstuffs (Table 5-1).

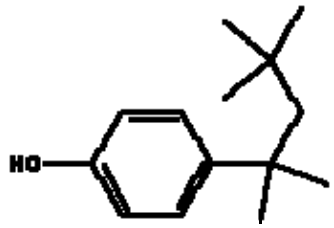
Table 5-1: 4-Nonylphenol (NP) concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Processed foods	Germany	0.1 - 19.4 µg/kg	Guenther et al. 2002
Fish and seafood	Taiwan	16.1 - 236 µg/kg	Lu et al. 2007
Meat	Taiwan	19.3 - 71.3 µg/kg	Lu et al. 2007
Vegetables	Taiwan	7.5 - 31.0 µg/kg	Lu et al. 2007
Fruits	Taiwan	22.0 - 27.4 µg/kg	Lu et al. 2007
In water			
Highest in Australian treated sewage	Australia	2.9 µg/L	This document
Highest expected in recycled water [1]	Australia	0.003 µg/L	Calculated from above value [1]
Drinking water	Germany	0.003 – 0.016 µg/L	Kuch and Ballschmiter 2001
Drinking water	China	0.01 – 2.7 µg/L	Campbell et al. 2006
Estimated daily intake (EDI)			
EDI from diet	Germany	7.5 µg/d	Guenther et al. 2002
EDI from diet	Taiwan	25.8 - 35.3 µg/d	Lu et al. 2007
EDI from diet	New Zealand	3.0 - 4.8 µg/d	Thomson et al. 2003
EDI from current drinking water [2]	Germany	Up to 0.032 µg/d	Calculated from above value [2]
EDI from recycled water [2]		Up to 0.006 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
TDI for 70-kg adult		10500 µg/d	This document
TDI for 10-kg child		1500 µg/d	This document
Recycled water guideline [3]	Australia	1000 µg/d	This document

[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.

Based on Table 5-1, the estimated daily intake (EDI) of NP from consumption of 2 L of recycled water is less than 0.2% of the dietary EDI.

4-t-Octylphenol



4-t-Octylphenol (4tOP) is also a by-product of alkylphenol polyethoxylate nonionic surfactants used in industrial processes. OP is estrogenic both *in vitro* and *in vivo* (Laws et al. 2000), and is roughly similar to NP in potency (Table 5-14). It is also produced in large amounts, and is likely to be found at high concentrations in food (much like nonylphenol).

Table 5-2: 4-t-Octylphenol (4tOP) in different compartments as well as estimated and tolerable daily intakes.

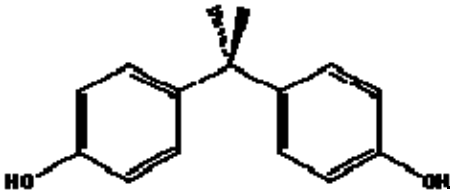
Compartment	Country	Concentration	Reference
Foodstuffs			
Seafood and fish	Singapore	6.7 – 44.9 µg/kg	Basheer et al. 2004
Seafood and fish	Italy	0.4 – 4.7 µg/kg	Ferrara et al. 2005
In water			
Highest in Australian treated sewage	Australia	0.014 µg/L	This document
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Germany	Up to 0.005 µg/L	Kuch and Ballschmiter 2001
Estimated daily intake (EDI)			
EDI from seafood diet only	Italy	0.05 µg/d	Ferrara et al. 2005
EDI from current drinking water [2]	Germany	Up to 0.01 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
TDI for 70-kg adult		1050 µg/d	This document
TDI for 10-kg child		150 µg/d	This document
Recycled water guideline [3]	Australia	100 µg/d	This document

[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.

Based on Table 5-2, the EDI of 4tOP from consumption of 2 L of recycled water is less than 4% of the dietary EDI from seafood alone.

Bisphenol A

Note that bisphenol A toxicity is covered in more details in section 5.3.1 – this section focuses on the estrogenic properties of bisphenol A.



Bisphenol A (BPA) is one of the highest volume chemicals produced worldwide, and is used in the production of polycarbonate plastics, epoxy resins used to line metal cans, and many plastic consumer products. It has been shown to be estrogenic both *in vitro* and *in vivo* (reviewed in Campbell et al. 2006). BPA can be found at high concentrations in processed foodstuffs due in part to leaching from consumer plastics and epoxy resin linings (Vandenberg et al. 2007). The liquid phase in canned vegetables contained as high as 450 µg/L in canned peas (Brotons et al. 1995), and the vegetables themselves containing BPA at concentrations as high as 95.3 µg/kg in canned corn (Yoshida et al. 2001). There are also less conventional sources of exposure to BPA. For example, BPA is used in dental sealants (as high as 670 µg/mg; Olea et al. 1996), and leaching can result in high concentrations of BPA in saliva (with up to 30 µg/mL of saliva 1 hour after application; Olea et al. 1996).

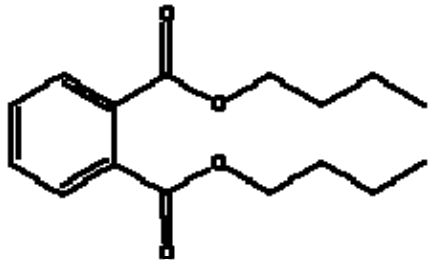
Table 5-3: Bisphenol A (BPA) concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Canned vegetables	Japan / USA	Up to 95.3 µg/kg	Yoshida et al. 2001
Infant milk formula		Up to 113 µg/kg	Campbell et al. 2006 [a]
Seafood and fish	Singapore	13.3 – 213 µg/kg	Basheer et al. 2004
Medical			
Dental sealant		5 – 670 µg/mg	Olea et al. 1996
In water			
Highest in Australian treated sewage	Australia	0.032 µg/L	This document
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Germany	0.002 µg/L	Kuch and Ballschmiter 2001
Drinking water	USA	0.02 – 0.04 µg/L	Campbell et al. 2006
Estimated daily intake (EDI)			
EDI from all sources for 70-kg adult	Europe	100 µg/d	EFSA 2006
EDI from all sources for 10-kg child	Europe	130 µg/d	EFSA 2006
EDI from current drinking water [2]	Germany / USA	Up to 0.08 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
TDI for 70-kg adult	Europe	3500 µg/d	EFSA 2006
TDI for 10-kg child	Europe	500 µg/d	EFSA 2006
Recycled water guideline [3]	Australia	400 µg/d	This document

[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.

Based on Table 5-3, the EDI of BPA from consumption of 2 L of recycled water is less than 0.1% of the overall EDI from all sources in a 70-kg adult or a 10-kg child.

di-n-Butyl phthalate



Phthalates are used in the production of various plastics and are among the most common industrial chemicals. Several million tons of these compounds, including di-n-butyl phthalate (DnBP), have been used as plasticizers for more than 40 years worldwide. Human exposure to phthalates occurs during production, distribution and final use of products made of PVC and other polymers because phthalates are easily released from the matrix (eg. plastic food wrap or food packaging) by evaporation and abrasion (Fromme et al. 2007). Food and consumer products (eg. cosmetics) are thus the main source of phthalates in humans (Wormuth et al. 2006). Phthalates have a very low estrogenicity relative to the natural hormone 17β-estradiol (Table 5-14), but humans can be exposed to very high concentrations.

Table 5-4: di-n-Butyl phthalate (DnBP) concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Total diet	Germany	10 – 124 µg/kg	Fromme et al. 2007
Total diet	UK	90 – 190 µg/kg	Petersen and Breindahl 2000
Baby food	UK	Up to 40 µg/kg	Petersen and Breindahl 2000
In water			
Highest in Australian treated sewage	Australia	Up to 0.89 µg/L	This document
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Spain	Up to 0.032µg/L	Casajuana and Lacorte 2003
Estimated daily intake (EDI)			
EDI from diet for 70-kg adult	Germany	8.4 – 114 µg/d	Fromme et al. 2007
EDI from all exposures for 70-kg adult	Germany	147 – 1960 µg/d	Wormuth et al. 2006
EDI from all exposures for 10-kg child	Germany	29 – 237 µg/d	Wormuth et al. 2006
EDI from current drinking water [2]		Up to 0.064 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
TDI for 70-kg adult	Europe	700 µg/d	EFSA 2005
TDI for 10-kg child	Europe	100 µg/d	EFSA 2005
Recycled water guideline [3]	Australia	70 µg/d	This document

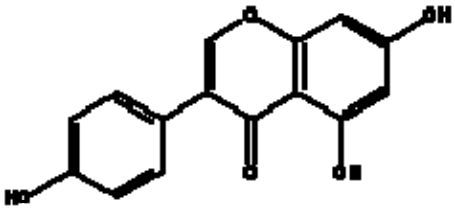
[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.

Based on Table 5-4, the EDI of DnBP from consumption of 2 L of recycled water is less than 0.02% of the dietary EDI in a 70-kg adult and less than 0.01% of the total EDI from all sources in a 70-kg adult or a 10-kg child.

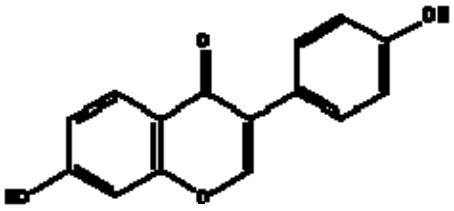
5.3.2.2 Phytosterols

Phytoestrogens are compounds produced naturally in plants that are estrogenic (Kuiper et al. 1998; Jefferson et al. 2002; Diel et al. 2004) and can cause estrogen-like effects in the animals that consume them, in the more severe cases leading to infertility (e.g. "clover disease" in sheep; Adams 1998). Phytoestrogens are relatively potent estrogen mimics (Table 5-14) and high amounts can be ingested through diet.

Isoflavones: Genistein and daidzein



Genistein



Daidzein

Genistein and daidzein, two potent isoflavone phytoestrogens, can be found at high concentration in leguminous plants, with concentrations as high as 841 000 and 560 000 µg/kg in soybean (Table 5-5 and Table 5-6; Mazur and Adlercreutz 1998). Plant-derived beverages such as beer and bourbon also contain high amounts of genistein and daidzein (Table 5-5 and Table 5-6; Lapcik et al. 1998).

Table 5-5: Genistein concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Soybean		841 000 µg/kg	Mazur and Adlercreutz 1998
Tofu	Japan	9000 µg/kg	Takamura-Enya et al. 2003
Chickpea		2140 µg/kg	Mazur and Adlercreutz 1998
Bread	UK	17100 µg/kg	Clarke and Lloyd 2004
Fish	UK	1200 µg/kg	Clarke and Lloyd 2004
Meat	UK	4400 µg/kg	Clarke and Lloyd 2004
Beer	Europe	0.05 – 1.8 µg/L	Lapcik et al. 1998
Beer	UK	Up to 23 µg/L	Clarke et al. 2004
In water			
Highest in treated sewage	Italy	0.083 µg/L	Lagana et al. 2004
Highest in treated sewage	Spain	0.007 µg/L	Farre et al. 2007
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Switzerland	< 0.002 µg/L	Erbs et al. 2007
Estimated daily intake (EDI)			
EDI from diet	UK	2260 µg/d	Clarke and Lloyd 2004
EDI from diet	Japan	Up to 30 000 µg/d	Fielden et al. 2003
EDI from current drinking water [2]		< 0.004 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]

[1] Based on a minimum 99.9% reduction from highest in European treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.

Table 5-6: Daidzein concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Soybean		560 000 µg/kg	Mazur and Adlercreutz 1998
Chickpea		1920 µg/kg	Mazur and Adlercreutz 1998
Bread	UK	5000 µg/kg	Clarke and Lloyd 2004
Fish	UK	300 µg/kg	Clarke and Lloyd 2004
Meat	UK	2300 µg/kg	Clarke and Lloyd 2004
Beer	Europe	0.02 – 0.65 µg/L	Lapcik et al. 1998
Beer	UK	Up to 13 µg/L	Clarke et al. 2004
In water			
Highest in treated sewage	Italy	0.016 µg/L	Lagana et al. 2004
Highest in treated sewage	Spain	Up to 0.012 µg/L	Farre et al. 2007
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Switzerland	< 0.001 µg/L	Erbs et al. 2007
Estimated daily intake (EDI)			
EDI from diet	UK	840 µg/d	Clarke and Lloyd 2004
EDI from current drinking water [2]		< 0.002 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]

[1] Based on a minimum 99.9% reduction from highest in European treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.

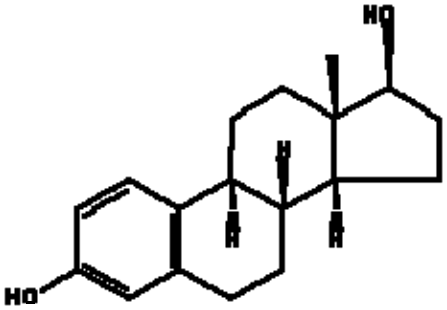
Based on Table 5-5 and Table 5-6, the EDI of genistein and daidzein from consumption of 2 L of recycled water is far less than 0.001% of the dietary EDI.

Other phytoestrogens

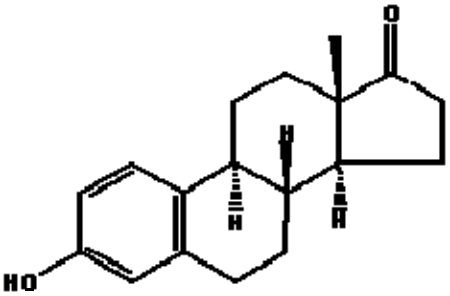
Plant-derived beverages such as beer and bourbon also contain other phytoestrogens such as β-sitosterol (Rosenblum et al. 1993), biochanin A (up to 33 µg/L; Clarke et al. 2004) and the very potent 8-prenylnaringenin (up to 138 µg/L; Clarke et al. 2004). Wine also contains high concentrations of resveratrol (red wine in particular, up to 3000 µg/L; Klinge et al. 2003).

5.3.2.3 Natural and synthetic estrogens

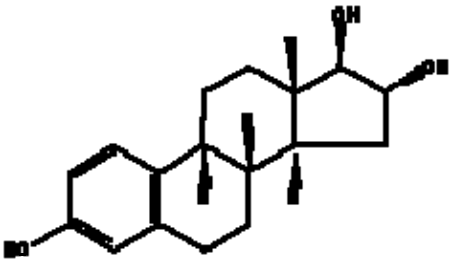
Natural hormones



17β-Estradiol



Estrone



Estriol

17β-Estradiol (E2) is excreted as glucuronide or sulfate conjugate in urine, but is deconjugated (re-activated) by microbial activity in the sewer and sewage treatment plants. Estradiol can thus be present in sewage (Table 5-7). Natural hormones including estradiol, estrone and estriol are also present in animal-derived foods such as meat or milk (Table 5-7).

Estrogens are produced daily by human endocrine systems, as high as 140 µg/d in men, 630 µg/d in pre-menopausal women, and 54 – 100 µg/d in pre-pubertal children (estradiol and estrone combined, Kushinsky 1983 cited in Hartmann et al. 1998). Under normal conditions, plasma estradiol concentrations are in the range of 0.01-0.06 µg/L in adult males and post-menopausal females and 0.03 - 0.4 µg/L in pre-menopausal females, although they can be as high as 0.35 - 2 µg/L during pregnancy (Tietz 1987; Holmes et al. 2000). In estrogen replacement therapy in post-menopausal women, estrogens (eg. estradiol or estrone sulfate) are prescribed at doses of approximately 500 - 2000 µg/day. Ingestion of this amount of estrogen can result in a 10-fold increase in plasma estrogen concentrations, bringing those to pre-menopausal levels (from an

average of 0.07 to 0.99, 0.05 to 0.48 and 0.55 to 8.23 µg/L for estrone, estradiol and estrone sulfate, respectively; Geisler et al. 1999).

Table 5-7: 17β-Estradiol (E2) concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Meat, untreated	France	0.003 µg/kg	Maume et al. 2001
Meat, treated with growth promoter	France	Up to 0.482 µg/kg	Maume et al. 2001
Poultry	Europe	Up to 0.73 µg/kg	Hartmann et al. 1998
Milk	Europe	Up to 0.06 µg/L	Hartmann et al. 1998
Medical			
Estrogen replacement therapy	Norway	2000 µg/pill	Geisler et al. 1999
In water			
Highest in Australian treated sewage	Australia	0.027 µg/L	This document
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Germany	Up to 0.002 µg/L	Kuch and Ballschmiter 2001
Estimated daily intake (EDI)			
EDI from dairy	The Netherlands	0.045 – 0.135 µg/d	Malekinejad et al. 2006
EDI from diet for 70-kg adult *	Europe	0.10 µg/d	Hartmann et al. 1998
EDI from diet for 10-kg child *	Europe	0.07 – 0.08 µg/d	Hartmann et al. 1998
EDI from current drinking water [2]		Up to 0.004 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
TDI for 70-kg adult	WHO	3.5 µg/d	JECFA 2000
TDI for 10-kg child	WHO	0.5 µg/d	JECFA 2000
Recycled water guideline [3]	Australia	0.35 µg/d	This document

[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.
* Combined EDI for 17β-estradiol and estrone.

Based on Table 5-7, the EDI of E2 from consumption of 2 L of recycled water is less than 2% of the dietary EDI in a 70-kg adult.

Table 5-8: Estrone (E1) concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Meat	Europe	Up to 0.28 µg/kg	Hartmann et al. 1998
Poultry	Europe	Up to 0.51 µg/kg	Hartmann et al. 1998
Milk	Europe	Up to 0.12 µg/L	Hartmann et al. 1998
In water			
Highest in Australian treated sewage	Australia	0.038 µg/L	LWA 2007
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Germany	< 0.001 µg/L	Kuch and Ballschmiter 2001
Estimated daily intake (EDI)			
EDI from diet for 70-kg adult *	Europe	0.10 µg/d	Hartmann et al. 1998
EDI from diet for 10-kg child *	Europe	0.07 – 0.08 µg/d	Hartmann et al. 1998
EDI from current drinking water [2]		< 0.002 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
Lowest therapeutic dose (LTD)		600 µg/d	This document
Recycled water guideline [3]	Australia	0.06 µg/d	This document

[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.
* Combined EDI for 17β-estradiol and estrone.

Based on Table 5-8, the EDI of E1 from consumption of 2 L of recycled water is less than 2% of the dietary EDI in a 70-kg adult.

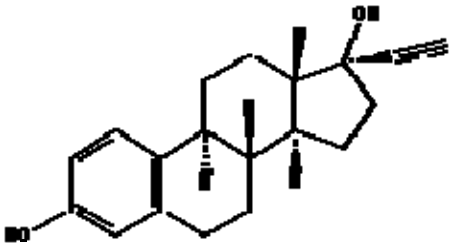
Table 5-9: Estriol (E3) concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Food stuffs			
Poultry	Europe	Up to 0.60 µg/kg	Hartmann et al. 1998
Milk	The Netherlands	Up to 0.012 µg/L	Malekinejad et al. 2006
In water			
Highest in treated sewage	USA	0.051 µg/L	This document
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Spain	< 0.005 µg/L	Lagana et al. 2004
Estimated daily intake (EDI)			
EDI from milk	The Netherlands	Up to 0.018 µg/L	Malekinejad et al. 2006
EDI from diet for 70-kg adult *	Europe	~ 0.01 µg/L	Based on Hartmann et al. 1998
EDI from current drinking water [2]		< 0.010 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
Lowest therapeutic dose (LTD)		1 000 µg/d	This document
Recycled water guideline [3]	Australia	0.1 µg/d	This document

[1] Based on a minimum 99.9% reduction from highest in treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.
* Estimated as $1/10^{th}$ of the combined EDI for 17β-estradiol and estrone from Hartmann et al. 1998.

An accurate EDI from other sources for E3 is not available. A rough estimation based on $1/10^{th}$ of the EDI of other estrogen hormones suggests that the EDI of E3 from consumption of 2 L of recycled water may be less than about 20% of the dietary EDI in a 70-kg adult.

Synthetic estrogens



Pre-menopausal women may also be exposed to very high concentrations of synthetic estrogens from birth control pills, which contain 20 – 50 µg of the very potent estrogen 17α-ethynylestradiol per pill, depending on the formulation.

Table 5-10: Ethynylestradiol (EE2) concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Medical			
Birth control pill		20 – 50 µg/pill	
In water			
Highest in Australian treated sewage	Australia	0.002 µg/L	LWA 2007
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Germany	< 0.001 µg/L	Kuch and Ballschmiter 2001
Estimated daily intake (EDI)			
EDI from birth control pill		20 – 50 µg/d	
EDI from current drinking water [2]		< 0.002 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
Lowest therapeutic dose (LTD)		30 µg/d	This document
Recycled water guideline [3]	Australia	0.003 µg/d	This document

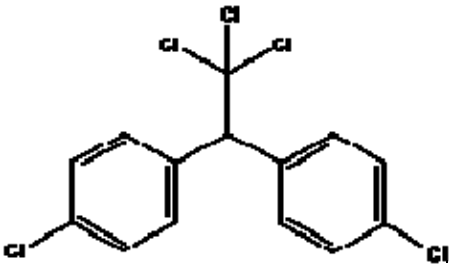
[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.

Based on Table 5-10, the EDI of EE2 from consumption of 2 L of recycled water is less than 0.01% of the EDI from birth control pills in pre-menopausal women.

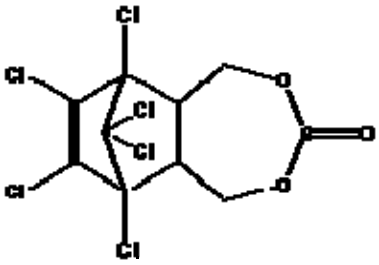
5.3.2.4 Personal care products

Some cosmetics can contain high levels of xeno-estrogens, and dermal exposure can result in absorption of these chemicals through the skin. Cosmetics such as deodorant, perfumes, aftershaves, shampoos and skin care products can contain very high concentrations of phthalates (as high as 10 000 µg/g DnBP in aftershave or nail care product for example; Wormuth et al. 2006). In the case of diethylphthalate, up to 80% of the estimated daily intake is caused by dermal application or incidental ingestion of personal care products (Wormuth et al. 2006). The alkyl esters of p-hydroxybenzoic acid (parabens) are also added in concentrations of up to 0.8% as preservatives to thousands of cosmetic products (Darbre 2006). Parabens can be absorbed rapidly through the skin (Darbre 2006) and they have weak estrogenic activity *in vitro* (Table 5-14). It is still unclear however what, if any, effect they might have in exposed humans (Darbre 2006).

5.3.2.5 Pesticides



p,p'-DDT



Endosulfan

Pesticides are used worldwide and provide significant benefits in agriculture. Pesticide residues in food do however pose risks to human populations, and they are closely monitored by food safety agencies (FSANZ 2003). Several pesticides such as DDT, endosulfan and dieldrin have been shown to possess estrogen-like activity both *in vitro* and *in vivo* (Bitman et al. 1968; Soto et al. 1994; Andersen et al. 2002).

Table 5-11: Total DDT concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Seafood	Australia	Up to 28 µg/kg	FSANZ 2003
Eggs	Australia	Up to 16 µg/kg	FSANZ 2003
Fish	Australia	Up to 22 µg/kg	FSANZ 2003
Ham	Australia	Up to 6 µg/kg	FSANZ 2003
In water			
Highest in Australian treated sewage	Australia	20 µg/L	This document
Highest expected in recycled water [1]		0.02 µg/L	Calculated from above value [1]
Drinking water	UK	< 0.005 µg/L	Quayle et al. 1997
Estimated daily intake (EDI)			
EDI from diet for 70-kg adult	USA	0.72 – 1.8 µg/d	Safe 1995
EDI from diet for 70-kg adult	Australia	0.035 – 0.042 µg/d	FSANZ 2003
EDI from diet for 10-kg child	Australia	0.007 – 0.01 µg/d	FSANZ 2003
EDI from current drinking water [2]		< 0.01 µg/d	Calculated from above value [2]
EDI from recycled water [2]		0.04 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
TDI for 70-kg adult	Australia	140 µg/d	FSANZ 2003
TDI for 10-kg child	Australia	20 µg/d	FSANZ 2003
Recycled water guideline [3]		2 µg/d	This document

[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.

Based on Table 5-11, the EDI of DDT from consumption of 2 L of recycled water can be equivalent to the EDI of DDT from dietary sources in a 70 kg adult in Australia. Note that this is based on a relatively high estimate of 0.02 µg/L of DTT in recycled water. The actual figure is likely to be lower.

Table 5-12: Endosulfan concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Vegetables	Australia	Up to 82µg/kg	FSANZ 2003
In water			
Highest in Australian treated sewage	Australia	0.25 µg/L *	This document
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	UK	< 0.005 µg/L	Quayle et al. 1997
Estimated daily intake (EDI)			
EDI from diet for 70-kd adult	USA	0.95 – 1.5 µg/d	Safe 1995
EDI from diet for 70-kg adult	Australia	0.161 – 0.182 µg/d	FSANZ 2003
EDI from diet for 10-kg child	Australia	0.025 – 0.033 µg/d	FSANZ 2003
EDI from current drinking water [2]		< 0.01 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
TDI for 70-kg adult	Australia	420 µg/d	FSANZ 2003
TDI for 10-kg child	Australia	60 µg/d	FSANZ 2003
Recycled water guideline [3]		60 µg/d *	This document

[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.
* Value is for endosulfan sulfate.

Based on Table 5-12, the EDI of endosulfan from consumption of 2 L of recycled water is less than 1.2% of the dietary EDI in a 70-kg adult.

5.3.2.6 Metallo-estrogens

Finally, some metals have also been shown to have estrogenic properties both *in vitro* and *in vivo*, particularly cadmium (Choe et al. 2003; Johnson et al. 2003). Food, rather than air or water, represent the major source of cadmium exposure, although tobacco smoking can significantly add to the body burden (FSANZ 2003).

Table 5-13: Cadmium (Cd) concentrations in different compartments as well as estimated and tolerable daily intakes.

Compartment	Country	Concentration	Reference
Foodstuffs			
Fish and seafood	Australia	Up to 500 µg/kg	FSANZ 2003
Vegetables	Australia	Up to 60 µg/kg	FSANZ 2003
Bread	Australia	Up to 230 µg/kg	FSANZ 2003
Meat	Australia	Up to 120 µg/kg	FSANZ 2003
Fruits	Australia	Up to 80 µg/kg	FSANZ 2003
In water			
Highest in Australian treated sewage	Australia	0.1 µg/L	This document
Highest expected in recycled water [1]		< 0.001 µg/L	Calculated from above value [1]
Drinking water	Germany	0.2 µg/L	Muller et al. 1996
Estimated daily intake (EDI)			
EDI from diet for 70-kg adult	Australia	4.9 – 20.3 µg/d	FSANZ 2003
EDI from diet for 10-kg child	Australia	1.8 – 6.8 µg/d	FSANZ 2003
EDI from current drinking water [2]		0.4 µg/d	Calculated from above value [2]
EDI from recycled water [2]		< 0.002 µg/d	Calculated from above value [2]
Tolerable daily intake (TDI)			
TDI for 70-kg adult	Australia	70 µg/d	FSANZ 2003
TDI for 10-kg child	Australia	10 µg/d	FSANZ 2003
Recycled water guideline [3]	Australia	4 µg/d	This document

[1] Based on a minimum 99.9% reduction from highest in Australian treated sewage by advanced water treatment systems and drinking water treatment (a conservative assumption).
[2] Based on consumption of 2 L/d of water containing highest expected concentration (described above).
[3] Based on the recycled water guideline recommended in this document and a 2 L/d consumption.

Based on Table 5-13, the EDI of Cd from consumption of 2 L of recycled water is less than 0.01% of the dietary EDI in a 70-kg adult or a 10-kg child.

5.3.2.7 Estrogenicity

The estrogenic activity of many of the above compounds has already been established in-vitro (Table 5-14). It is thus possible to roughly estimate the daily estrogenic intake (as estradiol equivalent, EEq) from both dietary sources and consumption of 2L of recycled water (Table 5-15), based on the data given in the tables above.

Table 5-14: Relative estrogenic potency compared to 17β-estradiol of estrogens and xeno-estrogens in an in-vitro MCF7 breast cancer cell proliferation assay.

Chemical	Relative estrogenic potency *	Reference
Steroid hormones		
17β-Estradiol (E2)	1	
Estrone (E1)	0.012	Leusch et al. 2006b
Estriol (E3)	0.071	Gutendorf and Westendorf 2001
Synthetic hormones		
Ethynylestradiol (EE2)	1.25	Gutendorf and Westendorf 2001
Diethylstylbestrol (DES)	2.51	Gutendorf and Westendorf 2001
Cosmetic additives		
Methylparaben	0.000 000 2	Byford et al. 2002
Ethylparaben	0.000 001	Byford et al. 2002
n-Butylparaben	0.000 022	Byford et al. 2002
Phytoestrogens		
8-Prenylnaringenin	0.033	Matsumura et al. 2005
Coumestrol	0.000 5	Matsumura et al. 2005
Genistein	0.000 5	Matsumura et al. 2005
Daidzein	0.000 05	Matsumura et al. 2005
Resveratrol	0.000 002 5	Matsumura et al. 2005
Industrial xeno-estrogens		
4-Nonylphenol (NP)	0.000 078	Leusch et al. 2006b
Bisphenol A (BPA)	0.000 03	Leusch et al. 2006b
4-t-Octylphenol (4tOP)	0.000 065	Leusch et al. 2006b
Benzyl butyl phthalate	0.000 002 4	Körner et al. 2001
di-n-Butyl phthalate (DnBP)	0.000 000 34	Körner et al. 2001
Metals		
Cadmium	0.009 7	Choe et al. 2003
Lithium	0.002 9	Choe et al. 2003
Pesticides		
p,p'-DDT	0.000 004	Fang et al. 2000
Endosulfan	0.000 001	Andersen et al. 2002
Dieldrin	0.000 000 2	Andersen et al. 2002

* Potency relative to 17β-estradiol.

Table 5-15: Estimated daily estrogenic intake (in estradiol equivalents, EEq) from dietary sources and recycled water (µg/d).

	DIET		RECYCLED WATER
Chemical	**Adult**	**Child**	**2 L/d**
4-Nonylphenol	0.0002 – 0.0028	< 0.0001 – 0.0004 [a]	< 0.0001
4-t-Octylphenol	< 0.0001	< 0.0001 [a]	< 0.0001
Bisphenol A	0.0030	0.0039	< 0.0001
di-n-Butyl phthalate	< 0.0001	< 0.0001 [a]	< 0.0001
Genistein	1.13 – 15.0	0.16 – 2.14 [a]	< 0.0001
Daidzein	0.0420	0.0060 [a]	< 0.0001
17β-Estradiol	0.1000	0.0700 – 0.0800	< 0.0020
Estrone	0.0012	0.0008 – 0.0010	< 0.0001
Estriol	0.0007 – 0.0013	0.0001 – 0.0002 [a]	< 0.0001
Ethynylestradiol	0 (37.5)[b]	0	< 0.0025
DDT	< 0.0001	< 0.0001	< 0.0001
Endosulfan	< 0.0001	< 0.0001	< 0.0001
Cadmium	0.0475 – 0.1969	0.0175 – 0.0660	< 0.0001
Total	**1.33 – 15.3 (52.8)[b]**	**0.26 – 2.30**	**< 0.005**

[a] EDI for child not available, estimated from adult EDI.
[b] Women taking birth control pill take an extra 37.5 µg/d estradiol equivalents.

Based on the data presented in the above tables (Table 5-1 to Table 5-14), the total estimated daily estrogenic intake in adults from dietary sources is 1.33 – 15.3 µg/d EEq, with 90 to 98% of the estrogenicity from dietary phytoestrogens (Table 5-15). A daily birth control pill adds 37.5 µg/d EEq, more than trebling the total daily estrogenic intake for pre-menopausal women. In children, the estimated daily estrogenic intake from diet is 0.26 – 2.30 µg/d EEq, with again a high proportion of that (70 to 93%) from dietary phytoestrogens. These figures are in agreement with previously published literature, which clearly highlights the significant intake of estrogenic chemical compounds from dietary phytoestrogens and contraceptives (Safe 1995; Pugh and Moore 1998).

In comparison, the estimated daily estrogenic intake from consumption of 2 L of recycled water results in less than 0.005 µg/d. This is much less than the dietary exposure, and in fact is only 0.01 – 0.35% of the exposure from diet in adults and 0.20 – 1.8% of the exposure from diet in children (note that in the absence of reliable age-related water consumption figures, childhood consumption was conservatively set at 2 L/d, the same as adults).

Other sources of exposures (eg. air) may also contribute to the total estrogenic intake. For example cigarette smoke extracts have been shown to be estrogenic *in vitro* (Takamura-Enya et al. 2003).

The estimated daily estrogenic intake from recycled water (expressed as 17β-estradiol equivalents, or EEq) is significantly lower than ADI of 3.5 µg/d for a 70-kg adult or 0.5 µg/d for a 10-kg child (JECFA 2000). However, the estimated daily estrogenic intake from dietary sources is more than 4 times higher than the ADI in both adults and children (and as high as 15 times higher for pre-monopausal women on birth control pills). The estimated estrogenic intake from dietary sources is in fact close to the daily production of endogenous estradiol in men (2-25 µg/d) or post-menopausal women (5-20 µg/d), although it is significantly lower than in pre-menopausal women (10-100 µg/d) (Williams and Stancel 1996).

5.3.2.8 Summary

When considering possible intake of xeno-estrogen compounds from recycled water, other sources have to be considered. When integrating several possible xeno-estrogenic chemical contaminants into an overall daily estrogenic intake, dietary intake (1.33-15.3 µg/d in adults and 0.23-2.30 µg/d in children) is significantly higher than the possible intake from consumption of 2L of recycled water (<0.005 µg/d). Contraceptives and dietary phytoestrogens constitute the large majority of the daily estrogenic intake in humans.

5.4 Conclusion

Water recycling carries with it the potential for the transmission of microorganisms, chemicals and other toxins directly to the consumer. It is for that reason that control of potential exposure at the source using HACCP (or similar risk management) principles will be the most effective means of control. Additional health surveillance should not be necessary in these circumstances.

As indicated in the case studies above exposure to chemicals in drinking water is unlikely to be the major source of exposure to these chemicals. Foodstuffs represent a much more likely source of exposure to a range of chemicals and contaminated air is an unavoidable source of modern urban exposure to chemicals. Doses of pharmaceuticals taken as part of normal therapy are greatly in excess of the concentrations of these pharmaceuticals found in treated drinking water.

In circumstances where the engineering controls and adoption of HACCP (or similar risk management) principles are applied to the production of treated drinking water augmented with recycled water, it is very unlikely that either anthropogenically derived or natural chemical contaminants will be found. The most likely outcome of a breakdown of any of these treatment processes, and poor contingency, emergency and incident plans, will be the release of untreated water and potential illness in the population utilising these water supplies. However, acute illness by the consumption of chemicals is extremely unlikely and chronic illness associated with long-term exposure to chemicals is also extremely unlikely because of the risk management processes associated with production of treated drinking water, an essential element of water quality management.

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Appendices.

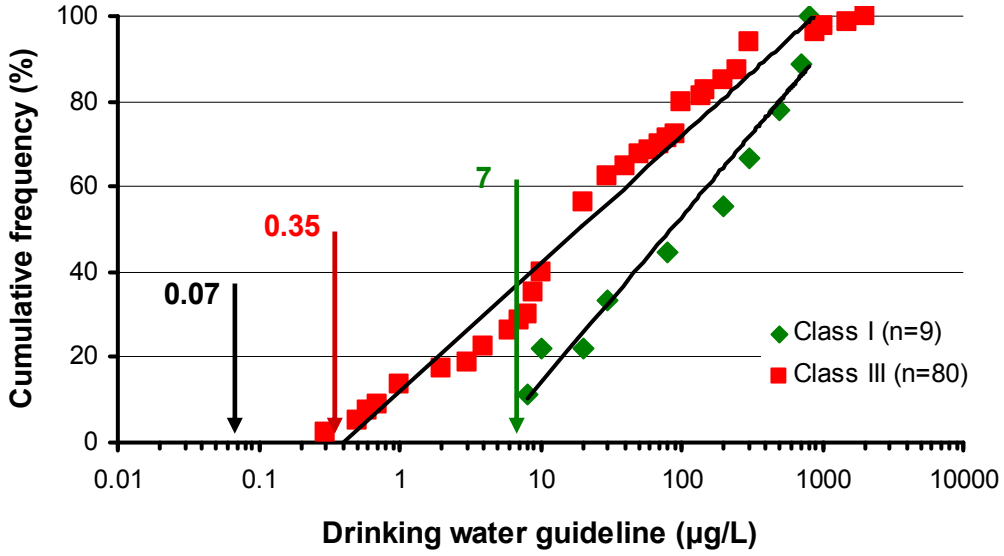
Appendix 1 (appendix to SECTION 2): Validation of the threshold of toxicological concern for drinking water standards.

To assess the validity of the Cramer class NOELs as assigned by Munro et al (1996) and others for use in setting drinking water guidelines, organic compounds for which there is a drinking water standard (from NHRC 2004 and WHO 2006) have been classified into the three Cramer classes using ToxTree. The following analyses were then undertaken:

1. The cumulative frequency of drinking water guideline for each of the Cramer classes was compared with the drinking water guideline established using the TTC for the classes (Figure A1-1).
2. Cumulative distributions of safety factors from the ADWG (NHMRC–NRMMC 2004) and WHO guidelines (2006) were applied to organic compounds when setting drinking water guidelines (Figure A1-2).
3. The frequency distribution of the known NOELs (used to set the drinking water standard) was compared to the NOELs for the same compounds in the Munro et al (1996) databases (Figure A1-3).
4. Compounds that have a drinking water guideline NOEL, and also a NOEL in the Munro database, were classified using ToxTree. The cumulative distributions of the Munro NOELs for Cramer classes I and III were then compared with the cumulative distributions of NOELs from the drinking water guideline database (Figure A1-4).

The classification of the drinking water organic chemicals from the ADWG (NHMRC–NRMMC 2004) and WHO (2006) fell neatly into class I or III. Only one chemical was classified into class II. When the respective basis of the drinking water guidelines (ie the NOELs) are compared, there is good agreement between the default NOEL used for the TTC and the experimental NOELs used to set the drinking water guidelines, indicating that the TTC concept applied to setting drinking water guidelines is a valid and protective process, just as it is for assessing minor contaminants in food.

Figure A1-1: Cumulative percentage frequency distributions of drinking water guideline values for compounds classified into Cramer classes I and III using ToxTree



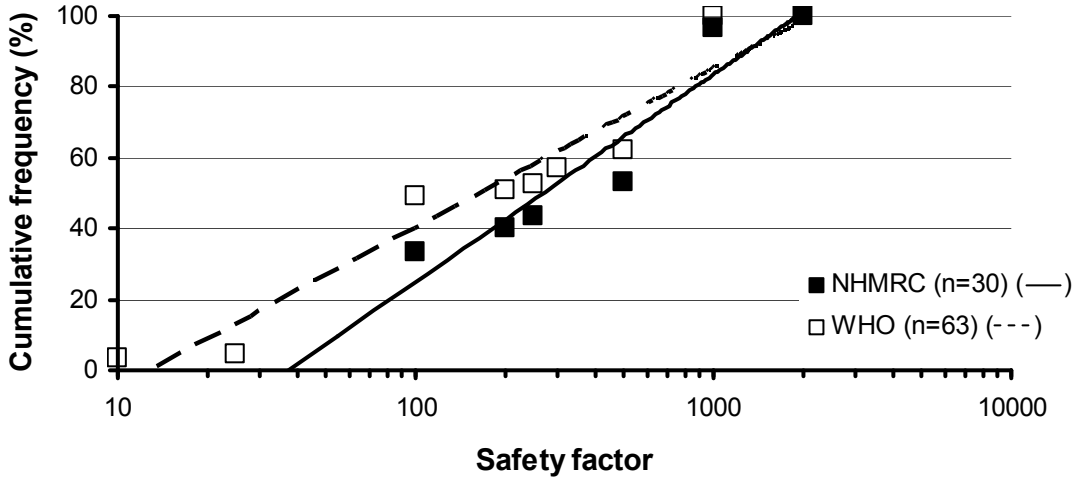
(For compounds of interest in recycled water ToxTree gave the same Cramer classification as Munro et al. 1996).

A logarithmic regression analysis of the cumulative per cent frequency data gives the following equations and coefficients of determination.
Regression equation for class I: Y = 16.904 Ln(x) + 91.887
R2 = 0.9564
Regression equation for class III: Y = 12.981 Ln(x) + 101.7
R2 = 0.9682
The black arrow represents the DWG set using the generic US FDA TTC of 0.02 µg/kg bw/day. The red arrow shows the DWG set using the 5th percentile NOEL for Cramer class III, ie 0.15 mg/kg/day.

The green arrow shows the DWG set using the 5th percentile NOEL Cramer class I, ie 3 µg/kg bw/day.

The DWG for class 1 & III substances were derived according to NHMRC procedure (Equation 1 of Box 2-3) with 10% as the proportion of intake allocated to drinking water and a safety factor of 1,500. The later was derived from analysis of the distribution of safety factors applied by NHMRC (2004) and WHO (2006) in setting drinking water guidelines from an experimental NOEL (Figure A1-2). The 95th percentile safety factor value by these organisations is respectively 1570 (n = 30 compounds) and 1660 (n = 63). A value of 1500 was chosen.

Figure A1-2: Cumulative distributions of safety factors applied by NHMRC-NRMMC (2004) and WHO (2006) to NOEL of organic compounds when setting drinking water guideline

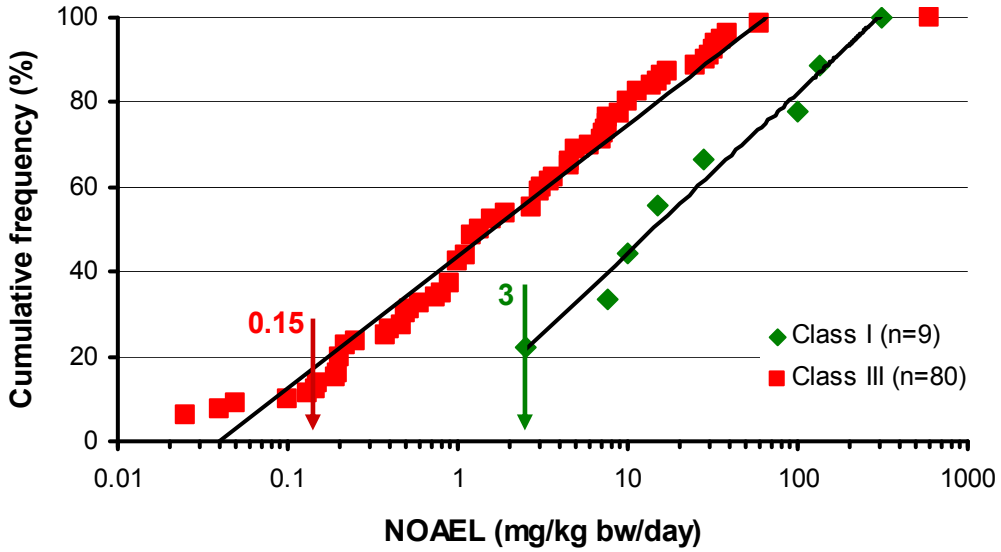


NHMRC: Regression equation: Y = 25.414 Ln(x) – 92.001
Coefficient of determination (R^2) = 0.9009
WHO: Regression equation: Y = 19.492 Ln(x) – 49.485
Coefficient of determination (R^2) = 0.9143

Descriptive statistics of safety factor distributions:

	Geometric mean	50th percentile	95th percentile
NHMRC	380	270	1,570
WHO	260	170	1,660

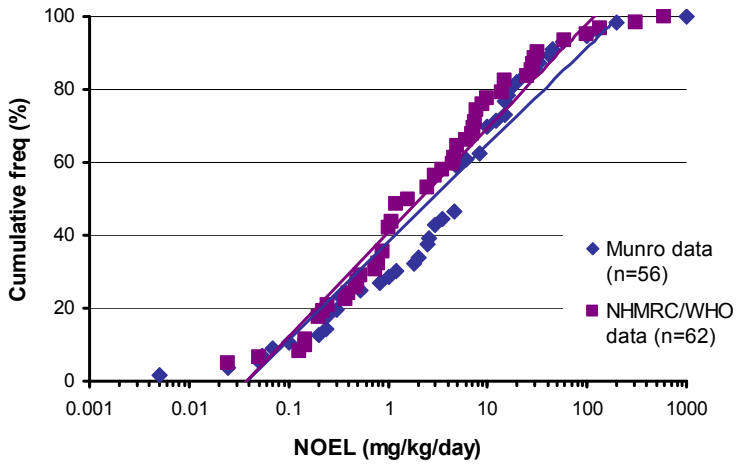
Figure A1-3: Cumulative frequency distributions of NOEL values for all organic compounds with a NHMRC or WHO drinking water guideline classified by ToxTree into classes I and III



A logarithmic regression analysis of the cumulative percent frequency data gives the following equations for each trend line and the following coefficients of determination.
Regression equation for class I: Y = 16.395 Ln(x) + 6.6987
R^2 = 0.9775
Regression equation for class III: Y = 13.505 Ln(x) + 43.658
R^2 = 0.9616
Also shown by the arrows are the NOEL values underpinning the TTC for Cramer class I and III.

Figure A1-4: Cumulative frequency distribution of Munro no observed effect levels (NOELs) and corresponding NHMRC and WHO NOELs for compounds with Australian and WHO drinking water guidelines

A.

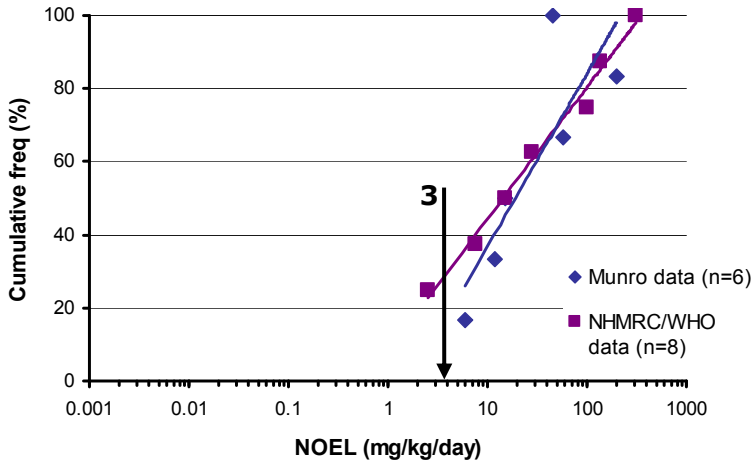


Regression equations:

Munro
Y = 11.615 Ln(x) + 37.995
(R^2 = 0.9288)

NHMRC/WHO
Y = 12.448 Ln(x) + 40.746
(R^2 = 0.9570)

B.

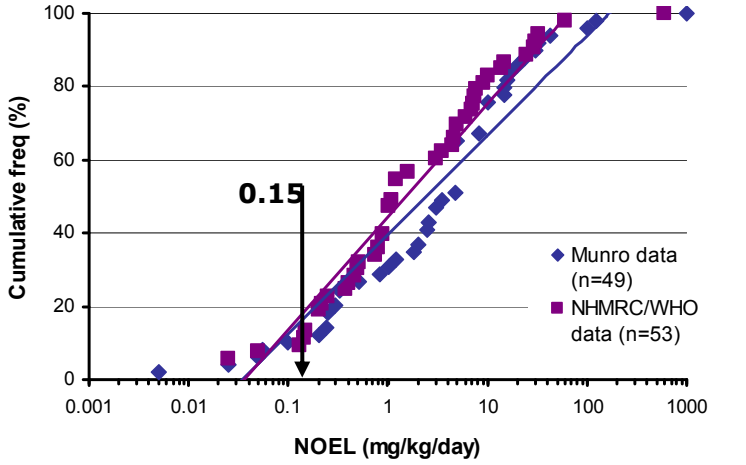


Regression equations:

Munro
Y = 20.592 Ln(x) – 10.71
(R^2 = 0.6991)

NHMRC/WHO
Y = 15.636 Ln(x) + 8.3364
(R^2 = 0.9877)

C.



Regression equations:

Munro
Y = 11.775 Ln(x) + 39.714
(R^2 = 0.9153)

NHMRC/WHO
Y = 13.367 Ln(x) + 44.296
(R^2 = 0.9434)

A. All compounds in common with Munro database.
B. Class I compounds (corresponding Munro TTC NOEL value indicated by arrow).
C. Class III compounds (corresponding Munro TTC NOEL value indicated by arrow).

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Appendix 2: CAS Registry Numbers

CASRN	Chemical Name	CASRN	Chemical Name
75-35-4	1,1-Dichloroethene (11DCE; 1,1-Dichloroethylene)	106-44-5	4-Methylphenol (p-Cresol)
611-59-6	1,7-Dimethylxanthine (Paraxanthine)	100-02-7	4-Nitrophenol
57-91-0	17α-estradiol	104-40-5	4-Nonylphenol (4NP)
57-63-6	17α-ethynylestradiol	140-66-9	4-tert-octylphenol
50-28-2	17β-estradiol	136-85-6	5-methyl-1H-benzotriazole
882-09-7	2-(p-Chlorophenoxy)-2-methylpropionic acid (Clofibric acid)	1506-02-1	6-Acetyl-1,1,2,4,4,7-hexamethyltetraline
38380-08-4	2,3,3',4,4',5-Hexachlorobiphenyl (PCB156)	98-86-2	Acetophenone
32598-14-4	2,3,3',4,4'-pentachlorobiphenyl (PCB105)	15972-60-8	Alachlor
31508-00-6	2,3',4,4',5-Pentachlorobiphenyl (PCB118)	319-84-6	α-BHC (alpha-BHC; alpha-lindane)
52663-72-6	2,4,5,3',4',5'-Hexachlorobiphenyl (PCB167)	12587-46-1	Alpha particles
88-06-2	2,4,6-Trichlorophenol (2,4,6-T)	28981-97-7	Alprazolam
81-15-2	2,4,6-Trinitro-1,3-dimethyl-5-tert-butylbenzene (musk xylene)	26787-78-0	Amoxycillin
94-75-7	2,4-D (2,4-Dichlorophenoxyacetic acid)	53-41-8	Androsterone
120-83-2	2,4-Dichlorophenol	23893-13-2	Anhydroerythromycin A
490-79-9	2,5-Dihydroxybenzoic acid	120-12-7	Anthracene
87-65-0	2,6-Dichlorophenol	7440-36-0	Antimony
719-22-2	2,6-di-tert-butyl-1,4-benzoquinone (2,6-bis(1,1-dimethylethyl)-2,5-Cyclohexadiene-1,4-dione)	60-80-0	Antipyrine
128-39-2	2,6-di-tert-butylphenol (2,6-bis(1,1-dimethylethyl)phenol)	7440-38-2	Arsenic
95-57-8	2-Chlorophenol	50-78-2	Aspirin (acetylsalicylic acid)
90-43-7	2-Phenylphenol	134523-00-5	Atorvastatin
32774-16-6	3,4,5,3’,4’,5’-Hexachlorobiphenyl (PCB169)	1912-24-9	Atrazine
72-55-9	4,4’-DDE	86-50-0	Azinphos-methyl
50-29-3	4,4’-DDT	83905-01-5	Azithromycin
13171-00-1	4-Acetyl-6-t-butyl-1,1-dimethylindan	7440-39-3	Barium
106-48-9	4-Chlorophenol	50-32-8	Benzo(a)pyrene
599-64-4	4-Cumylphenol	100-44-7	Benzyl chloride

CASRN	Chemical Name	CASRN	Chemical Name
319-85-7	β-BHC (beta-BHC; beta-lindane)	486-56-6	Cotinine ((S)-1-methyl-5-(3-pyridinyl)-2-Pyrrolidinone)
12587-47-2	Beta particles & photon emitters	91-64-5	Coumarin
63659-18-7	Betaxolol	50-18-0	Cyclophosphamide
41859-67-0	Bezafibrate (Benzafibrate)	52315-07-8	Cypermethrin
66722-44-9	Bisoprolol	67035-22-7	Dehydronifedipine
80-05-7	Bisphenol A	127-33-3	Demeclocycline
7440-42-8	Boron	126-75-0	Demeton-S
24959-67-9	Bromide	737-31-5	Diatrizoate sodium
7726-95-6	Bromine	117-96-4	Diatrizoic acid
79-08-3	Bromoacetic acid	439-14-5	Diazepam
83463-62-1	Bromochloroacetonitrile	333-41-5	Diazinon
74-97-5	Bromochloromethane	124-48-1	Dibromochloromethane
75-27-4	Bromodichloromethane	1002-53-5	Dibutyltin
75-25-2	Bromoform	79-43-6	Dichloroacetic Acid
4824-78-6	Bromophos-ethyl	3018-12-0	Dichloroacetonitrile
25013-16-5	Butylated hydroxyanisole (3-tert-butyl-4-hydroxy anisole)	75-09-2	Dichloromethane (Methylene chloride)
128-37-0	Butylated hydroxytoluene (2,6-Di-tert-Butyl-p-Cresol)	62-73-7	Dichlorvos
7440-43-9	Cadmium	15307-86-5	Diclofenac
58-08-2	Caffeine	42399-41-7	Diltiazem
57775-29-8	Carazolol	60-51-5	Dimethoate
298-46-4	Carbamazepine	84-74-2	Di-n-butyl phthalate
10605-21-7	Carbendazim		Dioxin like compounds (Total)
70356-03-5	Cefaclor	330-54-1	Diuron
15686-71-2	Cephalexin	564-25-0	Doxycycline
57-47-9	Chlordane	76420-72-9	Enalaprilat
7782-50-5	Chlorine	1031-07-8	Endosulfan sulfate
56-75-7	Chloramphenicol	93106-60-6	Enrofloxacin
67-66-3	Chloroform	517-09-9	Equilenin
120-32-1	Chlorophene	474-86-2	Equilin
57-62-5	Chlortetracycline	114-07-8	Erythromycin
2921-88-2	Chlorpyrifos	50-27-1	Estriol
5598-13-0	Chlorpyrifos-methyl	53-16-7	Estrone
7440-47-3	Chromium	563-12-2	Ethion
51481-61-9	Cimetidine	13194-48-4	Ethoprophos (Mocap)
85721-33-1	Ciprofloxacin	60-00-4	Ethylenediaminetetraacetic acid (EDTA)
81103-11-9	Clarithromycin	31879-05-7	Fenoprofen
37148-27-9	Clenbuterol	55-38-9	Fenthion (fenthion-methyl)
18323-44-9	Clindamycin	206-44-0	Fluoranthene
76-57-3	Codeine	16984-48-8	Fluoride
7440-50-8	Copper	54910-89-3	Fluoxetine
360-68-9	Coprostanol (5beta-Cholestan-3beta-ol)	13674-87-8	Fyrol FR 2 (tri(dichlorisopropyl) phosphate)

CASRN	Chemical Name	CASRN	Chemical Name
1222-05-5	Galaxolide	70458-96-7	Norfloxacin
25812-30-0	Gemfibrozil	3268-87-9	Octachlorodibenzo-p-dioxin
15687-27-1	Ibuprofen	79-57-2	Oxytetracycline
53-86-1	Indomethacin	103-90-2	Paracetamol
7553-56-2	Iodine	56-38-2	Parathion (ethyl parathion)
66108-95-0	Iohexol	298-00-0	Parathion-methyl (Methyl parathion)
60166-93-0	Iopamidol		PCBs (total)
73334-07-3	Iopromide	61-33-6	Penicillin G
3778-73-2	Isophosphamide	87-08-1	Penicillin V
22071-15-4	Ketoprofen	87-86-5	Pentachlorophenol (PCP)
7439-92-1	Lead	116-66-5	Pentamethyl-4,6-dinitroindane (Musk moskene)
154-21-2	Lincomycin	67-43-6	Pentetic acid
58-89-9	Lindane	85-01-8	Phenanthrene
121-75-5	Malathion	108-95-2	Phenol
7439-96-5	Manganese	85-44-9	Phthalic anhydride
72-33-3	Mestranol	57-83-0	Progesterone
657-24-9	Metformin (1,1-dimethylbiguanide)	525-66-6	Propranolol
59-05-2	Methotrexate	4408-81-5	(Propylenedinitrilo) tetraacetic acid (PDTA)
51218-45-2	Metolachlor	129-00-0	Pyrene
37350-58-6	Metoprolol	80214-83-1	Roxithromycin
7439-98-7	Molybdenum	18559-94-9	Salbutamol
17090-79-8	Monensin	69-72-7	Salicylic acid
78763-54-9	Monobutyltin (MBT)	7782-49-2	Selenium
81-14-1	Musk ketone	7440-22-4	Silver
145-39-1	Musk tibetene	122-34-9	Simazine
134-62-3	N,N-diethyltoluamide (N,N-diethyl-3-methylbenzamide) (DEET)	19466-47-8	Stigmastanol
42200-33-9	Nadolol	122-11-2	Sulfadimethoxine (SDMX)
389-08-2	Nalidixic acid (Negram, Naladixic acid)	57-68-1	Sulfamethazine (SMTZ)
91-20-3	Naphthalene	144-82-1	Sulfamethizole
22204-53-1	Naproxen	723-46-6	Sulfamethoxazole
7440-02-0	Nickel	599-79-1	Sulfasalazine
7697-37-2	Nitrate (NO_3^-)	72-14-0	Sulfathiazole
139-13-9	Nitrilotriacetic acid (NTA)	846-50-4	Temazepam
14797-65-0	Nitrite (NO2)	23031-25-6	Terbutaline
55-18-5	N-Nitrosodiethylamine	58-22-0	Testosterone
62-75-9	N-Nitrosodimethylamine	60-54-8	Tetracycline
59-89-2	N-nitrosomorpholine	23564-06-9	Thiophanate
25154-52-3	Nonylphenol	26839-75-8	Timolol
68-22-4	Norethindrone	13710-19-5	Tolfenamic acid

CASRN	Chemical Name	CASRN	Chemical Name
78-51-3	Tri(butyl cellosolve) phosphate (ethanol,2-butoxy-phosphate)	738-70-5	Trimethoprim
126-73-8	Tributyl phosphate	115-86-6	Triphenyl Phosphate
56573-85-4	Tributyltin	115-96-8	Tris(2-chloroethyl)phosphate
76-03-9	Trichloroacetic acid	1401-69-0	Tylosin
3380-34-5	Triclosan	7440-62-2	Vanadium
1582-09-8	Trifluralin		

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