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PHARMACEUTICALS AND PERSONAL CARE PRODUCTS IN THE ENVIRONMENT: A SUMMARY OF PUBLISHED LITERATURE

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NWRI Contribution No. 02-309

Volume 1 of 3

NATIONAL WATER RESEARCH INSTITUTE
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Pharmaceuticals and Personal Care Products in the Environment: A Summary of Published Literature

Produits pharmaceutiques et produits d'hygiène et de beauté dans l'environnement : Résumé de la littérature

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Management Perspective

Pharmaceuticals and personal care products in the environment is an emerging issue internationally. A wide variety of human and veterinary drugs and therapeutic products have been reported in surface and ground water around the globe. They enter the environment through a variety of waste management practices including municipal wastewater treatment, land application of sewage sludge and spreading of animal manures. Although they are generally considered to be biodegradable, significant quantities may be released directly in municipal effluents or indirectly through runoff from agricultural fields resulting in widespread exposure to the environment. Exposure of biota to these substances during critical life-stages may result in adverse effects. Very little data is available for the Canadian environment or drink water sources. Recently, these substances, regulated under the Food and Drugs Act were required to meet the environment assessment requirements under CEPA 1999. The federal government has committed to development of new regulations for this group of chemicals. This contribution, a working document, is a summary of the published literature organized in a way to facilitate an initial assessment of the potential fate, exposure, effects and risk of this diverse group of substances.

Sommaire à l'intention de la direction

La présence de produits pharmaceutiques et de produits d'hygiène et de beauté dans l'environnement devient un sujet de préoccupation à l'échelle mondiale. On a décelé une gamme étendue de médicaments et de produits thérapeutiques pour usages humain et vétérinaire dans les eaux de surface et les eaux souterraines du monde entier. Ces produits pénètrent dans l'environnement par diverses voies de gestion des déchets, y compris le traitement des eaux usées urbaines et l'épandage de boues résiduaires et de fumier. Même si ces produits sont généralement considérés comme biodégradables, il demeure que des quantités importantes peuvent se retrouver directement dans les effluents urbains ou indirectement dans l'environnement par la voie des eaux de ruissellement des terres agricoles. L'exposition du biote à ces substances aux stades critiques de la vie peut avoir des conséquences désastreuses. On dispose de très peu de données concernant cette forme de contamination de l'environnement et des sources d'eau potable au Canada. Récemment, le législateur a exigé que ces substances réglementées en vertu de la *Loi sur les aliments et drogues*, soient soumises aux critères d'évaluation environnementale de la LCPE de 1999. Le gouvernement fédéral s'est engagé à définir une nouvelle réglementation pour ce groupe de produits chimiques. Ce document de travail présente un résumé de la littérature organisé de manière à faciliter l'évaluation initiale du devenir potentiel de ce groupe diversifié de substances, de l'exposition de l'environnement et des effets et risques qui peuvent en découler.

Abstract

A wide variety of pharmaceutical and personal care products (PPCPs) are released to the environment through human wastewater and agricultural practices such as spreading of sewage sludge and animal wastes. Concern that PPCPs may be associated with environmental health effects was first raised in the early 1970s and has been echoed many times since. The widespread and continual introduction of these substances into surface waters at even very low concentrations may have the potential to cause a variety of adverse biological and ecological effects. Continuous or episodic exposure to these substances during sensitive life stages may result in subtle irreversible harm to the individual or the next generation.

This study was conducted to determine the current state of understanding of the environmental implications of continued low level releases and exposure of pharmaceutical ingredients and chemical ingredients in cosmetics and personal care products to the environment. Peer-reviewed published studies on the environmental effects of these chemicals, the availability of field-measured concentration data, as well as information on the environmental fate and physical chemical properties for chemical constituents of PPCPs were reviewed and summarized. As part of the study a PPCPs Database (Access) was developed to manage the information reviewed. Summary tables developed from the PPCPs Database were generated on:

- Parent Chemical Information (includes CAS no., Health Canada TPP ingredient code, Product use information);
- Parent Chemical and Breakdown Products via metabolism, biodegradation, photodegradation etc.;
- Absorption, Distribution, Metabolism and Excretion data (ADME);
- Physical Chemical data;
- Environmental Fate data
- Environmental Concentration data for various media (surface water; waste water; sediment; soil; biota; etc.)
- Environmental Effects data for various toxicological endpoints and biological species; and
- An Overview of Canadian and International (U.S. and EU) Policies Re: Environmental Assessment of PPCPs and their ingredients.

In addition, an electronic database of the references identified in the literature search was created (in ProCite) and provided in this report. It is anticipated that these PPCPs databases will need to be maintained and updated on an annual basis as new information on the environmental implications of PPCPs becomes rapidly available in the future. This area of study is in its infancy and further efforts in environmental monitoring, development of analytical detection methods and ecotoxicology are required to characterize the implications of low levels of PPCPs in the environment, especially in Canada. Data gaps and research needs identified, as part of this review will be presented and discussed elsewhere (Servos et al. in progress).

Résumé

Une gamme étendue de produits pharmaceutiques et de produits d'hygiène et de beauté (PPHB) parviennent dans l'environnement par la voie des eaux usées sanitaires et des pratiques agricoles comme l'épandage des boues résiduaires et du fumier. La possibilité que les PPHB soient à l'origine de problèmes d'hygiène du milieu a été soulevée la première fois au début des années 1970 et depuis, elle a été reprise maintes fois. Le déversement généralisé et continu de ces substances dans les eaux de surface même à très faibles concentrations peut engendrer une variété d'effets biologiques et écologiques néfastes. Une exposition continue ou intermittente à ces substances durant les stades critiques de la vie peut causer à l'individu intoxiqué ou à ses descendants immédiats un tort irréversible difficile à déceler.

Cette étude a été menée pour déterminer l'état actuel des connaissances sur les répercussions environnementales d'un rejet continu d'ingrédients pharmaceutiques et de composants chimiques de produits cosmétiques et d'hygiène personnelle en faibles concentrations et de l'exposition prolongée de l'environnement à ces produits. Les auteurs ont passé en revue et récapitulé les études fiables publiées sur les effets environnementaux de ces produits chimiques, les données de concentration mesurées *in situ* ainsi que l'information sur le devenir et les propriétés physico-chimiques des composants des PPHB. Dans le cadre de l'étude, une Base de données des PPHB (Access) a été élaborée pour permettre la gestion de l'information colligée. Des tableaux récapitulatifs ont été extraits de la Base de données des PPHB sur les sujets suivants :

- Information sur les produits chimiques parents (numéro de registre CAS, code PPT (Santé Canada) des ingrédients, Information sur l'usage des produits);
- Produits chimiques parents et produits de dégradation par métabolisation, biodégradation, photodégradation, etc.;
- Données sur l'absorption, la distribution, la métabolisation et l'excrétion (ADME);
- Données physico-chimiques;
- Données sur le devenir environnemental;
- Données de concentration dans l'environnement pour divers milieux récepteurs (eaux de surface, eaux usées, sédiments, sol, biote, etc.);
- Données sur les effets environnementaux pour divers paramètres toxicologiques et espèces biologiques;
- Aperçu des politiques canadiennes et internationales (É.-U. et Europe) concernant l'évaluation environnementale des PPHB et de leurs ingrédients.

De plus, les auteurs ont créé une base de références électroniques (sur logiciel ProCite) réunissant tous les sites répertoriés dans la recherche documentaire, liste reproduite dans ce rapport. On s'attend qu'il faudra assurer la mise à jour annuelle de ces bases de données sur les PPHB, au fur et à mesure que de nouvelles informations sur les effets environnementaux de ces produits deviendront disponibles. Ce domaine d'étude en est encore à ses débuts, et il faudra

consentir des efforts plus poussés de monitoring environnemental, de mise au point de méthodes d'analyse et d'écotoxicologie pour caractériser les répercussions des PPHB à faibles doses dans l'environnement, en particulier au Canada. Les lacunes dans les données et les besoins de recherches additionnelles cernés par les auteurs de cette étude seront présentés et commentés ailleurs (Servos et coll., en cours).

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February 1, 2002

1.0 Introduction

A scoping study was initiated to determine the state-of-the-art in scientific understanding of the implications of low levels of pharmaceuticals and personal care products (PPCPs) in the environment. Published peer-reviewed information was identified, reviewed and tabulated in an (Access) Database. Information was entered into the database that describe: the parent chemical; alternative chemical names; CAS number; for drugs the Health Canada TPP ingredient code; various breakdown products (daughter chemicals) and the breakdown pathway (e.g. metabolite, biodegradation product, photodegradation product); and the types of products of which respective chemicals are ingredients. As well the following data were input to the database: monitoring data of environmental concentrations of PPCPs; toxicity and environmental effects data for PPCPs; information on the analytical method; environmental fate; and physical chemical properties for chemical constituents of PPCPs. Tables summarizing the above information are presented based on a literature search conducted January 2000 and updated November 2001. An overview of Canadian and international (U.S. and EU) policies relevant to the requirement for environmental assessment of chemical ingredients used in human health and veterinary pharmaceutical products, and those used in cosmetics and personal care products has also been included that captures the current regulatory position as of late 2000.

The types of health care products addressed in the scoping study included human and veterinary pharmaceutical products, antibiotics, contrast agents and antiseptics, as well published data describing these products have been summarized in the PPCPs Database. Other health care products for human and animal use that may also be released to the environment in quantities that may warrant a concern include biologicals (e.g., vaccines, blood products), biotechnology products, medical devices, diagnostic ingredients, natural health products, foods, animal feeds. The types of cosmetic and personal care products reviewed include fragrances and flavour agents, ingredients of lotions, skin care products, oral hygiene, suncare products, shampoos and hair care products, soaps and detergents.

These types of products have been in mainstream consumer use and health care use for decades and are typically introduced into the environment as the parent chemical and the corresponding metabolites resulting from human or animal excretion by:

- discharge to municipal sewage treatment facilities of products and metabolites from consumer use followed by release of treated effluents to surface waters;
- discharge to municipal sewage treatment facilities and release to terrestrial environment through the land application of sewage-sludge;
- direct discharge to surface waters for communities lacking sewage treatment facilities;
- excretion by commercially raised animals directly onto agricultural soils and subsequent surface run-off to surface waters and leaching to groundwater;
- excretion by companion animals to soils and subsequent surface run-off to surface waters and leaching to groundwater;
- disposal of outdated or unused products to municipal sewage treatment facilities followed by release of treated effluents to surface waters;
- chemical ingredients are released to landfills through disposal of products as solid waste;
- direct introduction of parent and metabolites into sediments underlying fish farms or in treatment of waters from fish farms by local STP and application of resulting sewage sludge to agricultural land; and
- discharge of production waste materials to municipal sewage treatment facilities from pharmaceutical and cosmetic manufacturing facilities.

Another source of antibiotic release into the environment is through the burial of dead animals or fallen stock, and via the rendering of livestock and pets that have received antibiotics prior to their disposal (Klein, 1997) presenting a risk of both groundwater and surface water contamination.

Concern that PPCPs could be associated with environmental health effects was first raised in 1972 (Doving, 1991; Ross et al., 1992), and has been echoed many times since (Anonymous, 1989; Al-Ahmad et al., 1999; European Commission, 1999; Falter and Wilken, 1999; Koch, 1988; Lenski, 1993; Preuss and Ehrlich, 1987; Rorsova et al., 1977).

Pharmaceuticals used to treat humans and animals are excreted largely unchanged (Stan and Heberer, 1997) and hence enter municipal wastewater or the environment directly. Pharmaceutical products are of particular environmental concern since they are designed to affect specific metabolic pathways essential to life and are often intended to cause toxicity to target cells or organisms (Henschel et al., 1997; Jorgensen and Halling-Sorensen, 2000). Many

pharmaceuticals are designed to pass through biological membranes, thus must have some lipid solubility, are designed to have some degree of persistence so that they can effectively evoke the desired therapeutic response, and in many cases are produced in high volumes each year, (Halling-Sorensen et al., 1998b). Most pharmaceuticals are not released in volumes similar to those of major industrial chemicals, however, local environmental concentrations could occur at physiologically relevant concentrations. Estrogenic pharmaceutical products are used extensively in human estrogen-replacement therapy and oral contraceptives, and selective use in cancer chemotherapy. Veterinary uses of estrogenic substances are as growth enhancement products as well as reproductive therapeutic agents, and these hormones and their metabolites may enter the environment directly or via wastewater treatment effluents. Some pharmaceutical products, such as those used as growth promoters in livestock feed and on fish farms, and those used to prevent parasites on poultry farms may be released to the environment at rates similar to those of agrochemicals (Daughton and Ternes, 1999; Halling-Sorensen et al., 1998a). The occurrence and effects of endocrine disrupting substances, such as natural and synthetic hormones, was de-emphasized here as this subject has been comprehensively reviewed in the recent special issue of the Water Quality Research Journal of Canada (Servos and Van Der Kraak, Volume 36 No. 2, 2001).

It has been suggested that PPCPs could act as if they are persistent in the environment, even if they biodegrade due to their continual introduction to surface waters at low concentrations that results in constant life-cycle exposure to aquatic organisms (Daughton and Ternes, 1999). Concern has been expressed that subtle, low level cumulative effects occurring over time could cause irreversible change to ecosystems (Daughton and Ternes, 1999). Furthermore, persistent residues and degradation products may be released to surface waters via wastewater effluents. In some situations the flow of wastewater may contribute significantly to the combined flow of the receiving waters. Polar drug contaminants in surface water used for groundwater recharge may be a source of groundwater contamination with pharmaceuticals. A comprehensive review of much of the available data relevant to environmental risk assessment of PPCPs has been published (Daughton and Ternes, 1999).

The PPCPs Database may function as a key research and regulatory tool in the study of the implications of low levels of PPCPs in the environment by providing a consolidated reference database of relevant data. An annual updating of the PPCPs Access Database would be needed to

maintain this reference source as new information on PPCPs in the environment becomes available.

2.0 Materials and Methods

Literature Search

Relevant peer-reviewed literature on monitoring of pharmaceuticals and personal care products (PPCPs) in the environment and their potential effects on human and environmental health were identified through a dialog on-line search. Databases searched were Enviroline (40), Embase (73), Toxline (156), and Biological Abstracts (BA) (5). The search was conducted from 1985 to 2000 for Toxline, Embase and BA, and from 1998 to 2000 for Enviroline. A separate search was conducted using Medline.

All references and available abstracts were input electronically into ProCite 5 to create a searchable database of literature on PPCPs in the environment. Results of the literature search, identified >500 papers. References were previewed from titles and abstracts and those considered to be most relevant to the project were reviewed and summarized.

ACCESS Database

A PPCPs Access Database was designed to receive data summaries of the studies reviewed. The database holds information on: physical chemical properties; fate and bioaccumulation; toxic effects; and environmental concentrations in influents and effluents, surface water, soil, sediment, air, and biota; method of analyses; comments and references. The database is cross-referenced to the corresponding parent chemical and breakdown product (daughter chemical). Files contain information on the intended use of the chemical ingredient, short and long chemical name, CAS number, HC TPP Ingredient Code (drugs only), relationship of daughter chemical to parent (e.g. metabolite, biodegradation product, photodegradation product, etc.).

Pharmaceuticals - Mechanism of Action

Major groups of pharmaceuticals were established according to their known mechanism of action. Sources used were:

i) The Compendium of Pharmaceuticals and Specialties. 35th Edition. CD ROM Library 2000, Login Brothers Canada.

ii) Basic and Clinical Pharmacology. 3rd Edition. Edited by B.G. Katzung, MD, PhD. Appleton & Lange. A Publishing Division of Prentice-Hall. 1987.

Policies Relating to the Environmental Assessment of Pharmaceutical and Personal Care

Policies relating to the environmental assessment of pharmaceuticals and personal care products in Canada, the United States and Europe were identified through the on-line literature search, internet search, as well as through personal communication with key government departments. Personal communication with Health Canada was made with the following departments:

- Healthy Environments and Consumer Safety Branch (HECSB) – CEPA-NSD and CEPA-NSD-Biotechnology
- Cosmetics Program, Product Safety Bureau
- Therapeutic Products, Bureau of Policy & Coordination Therapeutic Products
- Bureau of Veterinary Drugs
- Office of Regulatory and International Affairs.

Personal communication with the U.S. Food and Drug Administration was made with:

- FDA/CFSAN/OCAC/HFS-101 – Cosmetics

Input from industry on the issue of environmental assessment of chemical ingredients of pharmaceuticals and cosmetics and personal care products was received from the Non-Prescription Drug Manufactures Association (NDMA), and the Canadian Cosmetic, Toiletry and Fragrance Association (CCTFA).

3.0 Results and Discussion

3.1 Sources of Pharmaceuticals and Personal Care Products to the Canadian Environment

There are 23,927 drugs with 3,336 ingredients listed in the Therapeutic Products Database of human and veterinary drugs approved for sale in Canada. Information on the identity of the major metabolites of these drugs should be available in the regulatory submissions for these drugs. There are 1,551 veterinary drugs approved for use in Canada, and for some of these, environmental risk assessments will have been conducted as part of the review process. In the US environmental assessment information from drug submissions is publicly available through the FDA Dockets Management Branch (Bloom and Matheson, 1993).

Additional information on major metabolites for food additives may be available in the regulatory submissions for these products or from the manufacturers. Information on metabolites of flavours and extracts used in foods may be contained in safety profiles prepared by the Flavour and Extract Manufacturers Association.

The primary source of human health and veterinary pharmaceuticals to the Canadian environment is through consumer use and animal use by excretion. Human health pharmaceuticals and their metabolites are discharged to municipal sewage treatment systems and subsequently released to receiving surface waters, or septic systems and may leach to groundwater. In some areas, primarily coastal areas, municipal sewage is discharged directly without treatment to oceans. Other environmental sources of pharmaceuticals related to consumer use occur during the disposal of outdated or unused products that may be disposed of to municipal sewers, or in the case of solid wastes that may be landfilled. Pharmaceuticals in landfills could be mobilized by leaching to groundwater. It should be noted that across Canada pharmaceutical disposal collection programs are operated by pharmacy associations, industry associations and municipalities and use licensed hazardous waste disposal facilities. Wastewaters of hospitals represent a potential concentrated source of drugs and their metabolites, particularly the potent cytotoxic antineoplastic agents used in chemotherapy and diagnostic agents. Considerably lesser amounts of pharmaceutical constituents may be released to the environment as waste from manufacturing facilities.

In Canada there are four major pharmaceutical manufacturers located in Toronto and Montreal, one in Winnipeg, and two in Vancouver. These facilities typically dispose of chemical waste materials to municipal sewers as per the plant operating license. Since these chemical ingredients are typically extremely expensive and safety practices are designed to minimize in plant exposures there is very little waste product generated by these facilities. Also, approximately 50% of domestically produced pharmaceuticals are exported to the US and elsewhere.

Veterinary pharmaceuticals may be used prophylactically among large numbers of food producing animals as performance enhancements in animal feeds or for therapeutic use in individual animals. Excretion of the parent and metabolites often results in direct introduction to the terrestrial environment with subsequent introduction to surface waters via surface run-off or via leaching to groundwater. Other chemicals used in veterinary operations such as diagnostic agents, pesticides, dips and tars, etc. are potentially released to the environment during their use and their disposal. The use of pharmaceuticals in farmed fish feed may present a direct release to the environment (i.e. surface waters and incorporation into sediments beneath fish enclosures) or an indirect release for fish operations that pump waters to municipal sewers for treatment prior to their release.

The primary source of personal care products to the Canadian environment is through consumer use and disposal of outdated or unused products directly to municipal wastewater systems or landfills.

3.2 Estimation of Releases of Pharmaceuticals and Personal Care Products to the Environment

No information on the release or use rates in Canada of any PPCPs was identified in the literature or on the Internet. There is no federal repository of information on the production volumes, import volumes or patterns of use of human health and veterinary pharmaceuticals and cosmetics in Canada. Typically Health Canada does not collect this type of information. Neither were the industry associations, NDMAC and CCTFA, able to provide these data. The Therapeutic Products Programme (TPP) does maintain a database of pharmaceutical products available for use in Canada. The TPP database includes information on the active and excipient ingredients of each product and the typical dosage, frequency and duration of treatment. This information could be used to calculate the amount of product used per individual from which the daily release to municipal sewage system could be estimated.

Comprehensive data on prescription rates for human pharmaceuticals are available through IMS Canada Ltd and these data can be obtained on a municipal, regional or national basis. Canadian national annual sales-in data (i.e. amount of product purchased for sale per year) for community pharmacies and hospitals for prescription and OTC products have been requested by Environment Canada for the top 500 drug products (not presented here). This information will provide an indication of the type and amount of drugs that are most widely used in Canada and therefore likely to enter the environment in greater amounts. Predicted release rates for veterinary pharmaceuticals may be available in the regulatory submissions for those products that required an environmental assessment to be conducted as part of the approval process.

3.3 Chemical Specific Information Entered into PPCPs Access Database

Table 1 outlines the tables in this report printed from the PPCPs Access Database, February 1, 2002. There are greater than 50 groupings of pharmaceutical ingredients on the basis of similarities in therapeutic effects or mechanisms of action. While in some cases understanding the characteristics of a prototype drug can enable inference of the characteristics of other agents in the same drug group, for many therapeutic drugs the mechanism of action is largely unknown (Katzung, 1987). There is equal if not greater uncertainty in regard to the environmental toxicity of pharmaceutical agents belonging to the same or different drug group. The current knowledge

base of the environmental toxicology of pharmaceutical agents is not sufficient to presume that the toxicity of one agent can be readily assumed on the basis of limited toxicity information of another drug agent belonging the same group. For example, many pharmaceuticals can modify pituitary hormone secretion (Crisp et al., 1998). This may occur either by direct action of synthetic/natural steroids on the pituitary (e.g. estrogen, diethylstilbesterol), or by indirect action of agents on pituitary receptors or of agents that affect neuropeptide or neurotransmitter regulation of releasing factors (e.g. Selective Serotinin Reuptake Inhibitors - SSRIs). For most pharmaceutical products the potential environmental effects on aquatic, benthic and terrestrial non-target organisms are unknown. It is possible that toxicity of some drugs in aquatic ecosystems may be different or unrelated to the therapeutic mechanism of action of pharmaceuticals in humans and domestic animals.

The major classes of pharmaceutical agents for which environmental monitoring and/or effects data have been published in the scientific literature are summarized in Table 2. An overview of the PPCPs for which environmental monitoring and/or environmental effects data was identified and reviewed is provided in Tables 3a and 3b. Further research is required to elucidate a common mechanism of toxicity across the classes of drug ingredient. Some insight into toxicity and environmental fate may be gained through the use of physical-chemical properties and Quantitative Structure Activity Relationships (QSARs); however for the majority of pharmaceuticals entered into the PPCPs Access Database these physical-chemical data were considered to be proprietary and not readily available for review. Pharmaceutical and personal care ingredients that have been entered into the PPCPs Access Database are summarized in Tables 4 and 5. These tables provide information on the chemical short- and long-name, use, and CAS no., as well as the relationship between the parent and daughter chemicals. Information on the absorption, metabolism and excretion is provided in Table 6. Physical-chemical data identified in the published literature and entered into the PPCPs Access Database are presented in Table 7.

3.4 Environmental Monitoring and Effects Data

The review identified a paucity of Canadian environmental monitoring data of PPCPs. The vast majority of environmental monitoring studies have been conducted in Germany, Sweden and Switzerland with some studies in Japan.

Tables 3a and 3b provide an overview of the PPCPs for which environmental concentration data and/or environmental effect data were identified in the published literature reviewed. In terms of environmental effects, the majority of the data reviewed was for short-term acute toxicity in standard test aquatic organisms (see Figure 1). There were few long-term chronic effects data nor *in-situ* ecosystem effects monitoring data, with the exception of some studies of estrogenic effects observed in feral and caged fish downstream of wastewater effluents (see Figure 2). A few 21-day reproduction studies in Daphnia for selected chemicals and a 14 day LC50 in fish exposed to nitro musks were identified (see Figure 2). The data were insufficient to enable general conclusions regarding the chronic toxicity of any one particular drug or drug group. The most potent chemicals that were identified that are capable of inducing responses in aquatic organisms at ppb concentrations and lower include:

- SSRIs (antidepressants) have been demonstrated to induce effects on gonad development in aquatic invertebrates at very low levels; no toxicological information was identified for SSRIs in other aquatic or terrestrial non-target organisms. No information was identified in the published literature on the physical chemical properties, environmental fate or environmental concentrations of SSRIs;
- Hormones (e.g. synthetic and natural estrogens) have been found to induce estrogenic effects in male fish exposed to wastewater effluents; and
- Antiparasitic/antiprotozoal agents which were most potent in aquatic invertebrates.

Antibiotics used in human health and veterinary therapy as well as animal feed additives are recognized as an environmental concern primarily attributed to problems related to the development of antibiotic resistance in microorganisms, and their bactericidal affect in waste water treatment systems.

Antineoplastic drugs used in cancer treatment as these drugs are by design cytotoxic, are relatively non-metabolized by the patient, and have some lipophilic properties to enhance transmembrane uptake. Little information was identified on the acute toxicity of the antineoplastic drugs and no information on the chronic toxicity of antineoplastic agents in aquatic organisms was identified. Furthermore, there was little or no information identified in the published literature on the environmental fate and environmental concentrations of many antineoplastic agents. This was the case for many other pharmaceutical ingredients.

With respect to personal care products, the greatest amount of data relating to the environment was for the musks. Natural and synthetic musk compounds are used widely as fragrances in consumer products such as cosmetics, toiletries, detergents, soaps, toothpastes, as flavours in the food industry, in fish farming, and in pharmaceuticals. These compounds are therefore ubiquitous and have been detected throughout the world in surface waters, sewage, sediments and fish of contaminated rivers and estuaries (Draisci et al., 1998). Recently the polycyclic musks have been the focus of environmental monitoring studies in Europe (Balk and Ford, 1999a; Balk and Ford, 1999b; Rimkus, 1999; Tas et al., 1997). Their toxicological potency is relatively unknown.

Some nitro-containing fragrances such as musk ambrette, musk xylene and musk ketone have been found to be mutagenic and genotoxic [Emig et al 1996 as cited in (Mersch-Sundermanno et al., 1998) (Ippen, 1994)]. Musk xylene and musk ketone are strong inducers of xenobiotic detoxifying liver enzymes [Mersch-Sundermann et al., 1996b as cited in (Mersch-Sundermanno et al., 1998)]. Musk xylene and musk ketone are the major nitro musks detected in the environment. Nitro musks, first identified in the aquatic environment in 1981 in some Japanese waters (Yamagishi et al., 1981, 1983 cited in Rimkus et al., 1999), are highly bioaccumulative (Rimkus et al., 1999). Due to its bioaccumulative propensity, musk xylene was banned in Japan as an ingredient in domestic products (Maekawa et al., 1990 as cited in Rimkus et al., 1999), and in 1993 a partial phase-out of musk xylene was agreed to by the German cosmetic and detergent industry association (Rimkus and Brunn, 1996, and Brunn and Rimkus, 1997 cited in Rimkus et al. 1999). Since 1994, efforts have been taken by the fragrance industry in Switzerland to reduce the amount of musk xylene in detergents and cleaning agents. The use of musk ambrette was banned in the EU in 1995 and it has been included in the list of banned components in cosmetics (Berset et al., 2000). As of 1998, musk ambrette has been forbidden in Switzerland. Musk xylene

and musk ketone, were included in the EU third priority (Rimkus, 1999). Under leadership of the Netherlands and environmental risk assessment for musk xylene and musk ketone was undertaken (Tas et al., 1997). Musk xylene is also included in the OSPAR List of Chemicals for Priority Action [OSPAR convention for the protection of marine environment of the northeast Atlantic. Sept. 14-16, 1998, Berlin; Anonymus, 1998 as cited in (Rimkus, 1999)].

There is a paucity of ecotoxicology data on mixed amino nitroaromatics (e.g. nitro musk fragrances) (Rimkus et al., 1999). Only one study in an aquatic invertebrate was identified on the ecotoxicological effect of these mixed amino nitroaromatics in the aquatic environment (Rimkus et al. 1999). Furthermore the toxicity of the metabolite $4NH_2$-MX was reported to be more than 1000 times greater than the parent compound (Behechti et al., 1998; Tas et al., 1997).

Commonly used pigments are characteristically insoluble in aqueous solution which complicates toxicity studies (Moller and Wallin, 2000). More information is needed on the uptake, genotoxicity, and metabolism of pigments for the assessment of ecotoxicological effects (Moller and Wallin, 2000).

The possibility of additive or potentiative toxicity of PPCPs in aquatic organisms needs to be addressed when assessing the potential environmental effects of wastewater constituents. For example, estrogenic substances and the SSRIs have been independently observed to affect gonadal development in aquatic organisms. The result of their combined exposure at environmental concentrations in aquatic organisms, including different trophic levels, is unknown. Another example is the potential additivity of the nitro musks and their metabolites (Rimkus et al., 1999) which warrants more in-depth environmental analysis and toxicological studies of both parent compounds and metabolites.

Data reviewed on the environmental fate of PPCPs are summarized in Table 8. Environmental concentration data reviewed and entered into the PPCPs Database has been summarized in Table 9. This information includes the media type, concentration, location and analytical methodology used and reference. Environmental effects data obtained through standard laboratory testing and ecosystem monitoring and a description of the test organism and study methods have been summarized in Table 10.

3.5 Environmental Assessment Policies

Table 11 compares the policies for requirement of environmental assessment of human health pharmaceuticals, veterinary drugs, cosmetics and personal care products, biotechnology products and food additives in Canada, the U.S., the EU, and some information on the registration of veterinary drugs in Australia and New Zealand. Overall, Canada appears to have minimal requirements for product registration of PPCPs pertaining to the environmental assessment of these products and their chemical ingredients. In the past no formal environmental assessment has been required as part of the regulatory process for human health and veterinary pharmaceuticals, or cosmetics and personal care products in Canada. The Health Canada policy relating to the environmental assessment of health products is currently under discussion with respect to Health Canada's obligation under the Canadian Environmental Protection Act (CEPA) (Health Products and Food Safety Branch, Healthy Environments and Consumer Safety Branch, June 25, 2001). Human health drugs, cosmetics and personal care products, and biotechnology products in Canada are covered by the Food and Drug Act and thereby were categorically exempt from the Canadian Environmental Protection Act (CEPA) until 1999. Since then all substances new to Canada are subject to CEPA, 1999 and require environmental assessment under New Substance Notification (NSN) of CEPA, 1999. Thus today any new pharmaceutical ingredient to Canada would theoretically require environmental review in accordance with CEPA, 1999. Proposed draft guidelines, December 2000, for the environmental assessment of new biotechnology products have been outlined by Health Canada (Health Canada, 2000). The Healthy Environments and Consumer Safety (HECS) Branch of Health Canada maintains a New Substance Division (NSD) with two programs: 1) new chemical; 2) biotechnology with substance review of health effects of an environmental assessment. Until recently, Health Canada provided for only human health assessment of these substances. Future Health Canada Environmental Assessment Regulations (if promulgated) would provide for pre-market environmental assessment. However, environmental risk management is primarily a function of Environment Canada under CEPA.

In contrast, environmental assessment is required in the US for the registration of human health pharmaceuticals using a tiered approach and a case-by-case approach is used for veterinary drugs. In the EU, Australia and New Zealand, registration of veterinary products requires some level of environmental assessment. A similar approach for the environmental assessment has been recently proposed in the EU for human health pharmaceutical products.

There are presently no regulatory requirements for formal environmental assessment of chemical ingredients used in cosmetics and personal care products in any country. In Canada new substances to Canada used in cosmetics and personal care products would be subject to environmental review under CEPA 1999.

4.0 Conclusions

This area of study of low levels of pharmaceutical and personal care products in the environment is in its infancy and further effort is required to identify PPCPs of environmental concern. Information on the fate, effects, environmental release/use and the respective environmental concentrations is needed to conduct qualitative/quantitative environmental risk assessments. Data gaps and research needs are discussed in detail elsewhere (Servos et al. to be submitted to the Water Quality Research Journal of Canada *in progress*). Annual updating of the PPCPs Access Database would maintain this as a valuable reference for research and regulatory assessment of pharmaceuticals and personal care product ingredients released to the Canadian environment.

5.0 Acknowledgements

This work was supported by the National Water Research Institute, Environment Canada and the Office of Regulatory and International Affairs, Health Products and Food Branch, Health Canada.

Table 1: Overview of Summary Tables from PPCPs ACCESS Database presented in this NWRI report.

Table 1: Overview of Summary Tables from PPCPs ACCESS

Table No.	Table Title and Contents	No. of Pages
Table 4:	Parent Chemical Information – parent chemical short and long name; CAS no.; HC TPP Ingredient Code; uses health; no. of health products; uses personal care; uses other; reference.	35
Table 5:	Parent Chemical/ Breakdown Product Relationship – parent chemical short and long name; breakdown product short and long name; relationship (e.g. metabolite, biodegradation product); reference.	3
Table 6:	Summary of Absorption/ Metabolism/Excretion Data – parent chemical or break down product; data type (e.g. metabolism); data; test matrix, method/parameters; reference.	3
Table 7:	Summary of Physical-Chemical Data – Parent chemical or breakdown product; data type (e.g. vapor pressure, water solubility); data; method/parameters; reference.	6
Table 8:	Summary of Environmental Fate Data – parent chemical or breakdown product; data type (e.g. biodegradation, Low, BAF); data; test matrix; method/parameters; reference	15
Table 9:	Summary of Environmental Concentrations – parent chemical or breakdown product; descriptor (e.g. soil; surface water; waste water effluent); data; test matrix; method/parameters; country; reference	52
Table 10:	Summary of Effects Data – parent chemical or breakdown product; data type (effect, acute effect, subchronic effect); descriptor (e.g. EC50, LC50, NOEC); data; test matrix; method/parameters; reference.	28

Table 2: Summary of Major Pharmaceutical Drugs Groups Reviewed in the Environment

Table 2: Summary of Major Pharmaceutical Drugs Groups Reviewed in the Environment

Major Drug Group	Action/Use	Examples of Drugs Belonging to Group
Antibiotic	Kills or inhibits growth of bacteria; specific action depends on type of antibiotic; used to treat bacterial infections; used as animal feed additive to enhance growth; use in fish farming to control disease.	penicillin; tetracyclines; chloramphenicol; ciprofloxin; furazolidone; streptomycin
Antineoplastic agents	Cytotoxic; mutagenic; genotoxic; attacks cancerous cells; use in chemotherapy various cancers, rheumatoid disorders	mitomycin; cyclophosphamide methotrexate
Hormones (natural and synthetic)	Sex hormones to treat/control reproduction system; feed additives in animal food industry; steroids to treat auto-immune disorders; treat skin disorders	estrogen; estradiol; estrone; ethinyl estradiol; DES; testosterone; corticosteroids; moxestrol
NSAIDs (non-steroidal anti-inflammatory drugs)	anti-inflammatory (to treat inflammation and rheumatic diseases); analgesics; anti-pyretic.	ASA; acetaminophen; ibuprofen
Antidepressant –tricyclic	Treat depression disorders; chronic pain; enuresis; other phobias	amitriptyline
Anti-depressant SSRIs (selective seritonin re-uptake inhibition)	Treat depression related disorders	fenfluramine hydrochloride; fluoxetine; fluvoxamine; paroxetine
Cardiac drug-antihypertensive	Calcium channel blocker; antiarrhythmia and antiangina; lower blood pressure	veraparmil
Cardiac glycoside	Treat congestive heart failure	digoxin
Lipid-lowering agents	Treat hyperlipidemia	clofibrate; nicotin
Sedative hypnotics-antiepileptic agents	Treat manic depression; epilepsy	diazepam
Beta-blockers	Block beta receptors; lower blood pressure; local anesthetic effect; treat hypertension; treat ischemic heart disease and cardiac arrhythmias; treat glaucoma; treat hyperthyroidism	Propanolol; nadolol
Neurotransmitters	Treat neurological disorders	leva dopa; norepinephrine; serotonin
Antiparasitic/antiprotozoal	To kill parasites veterinary use and human use	amprolium; bromocyclen; ivermectin; metronidazole
x-ray contrast agent	Diagnostic imaging	iohexol; iopromide
Chelating agents	Treat heavy metal poisoning; excipient ingredient in drugs and cosmetics	EDTA; DPTA; [S,S]-EDDS
Disinfectants/Antiseptics	Bacteriocidal/bacteriostatic treat surfaces	Phenol; benzaldehyde (preservative)

Table 3a: Overview of Environmental Monitoring and Effects Data Reviewed - Pharmaceuticals

Table 3a: Overview of Environmental Monitoring and Effects Data Reviewed - Pharmaceuticals

Pharmaceutical Chemical Ingredient	Environmental Detection				Toxicity (aquatic)	
	ww	sw (gw,dw)	sed/sldg	biota	acute	subchronic
16a-hydroxystrone	•					
2,4,6 –tribromophenol	•	•				
4-chloroxylenol	•	•				
4-nonylphenol	•		•			
4-tert-octylphenol	•		•			
dialylbarbituric acid		-/gw				
acetaminophen	•				• algae, invertebrates, fish	
amitriptyline					• invertebrate	
ampicillin						antibiotic resist. bacteria
amprolium						NEL antimicrobial effects
androsterone	•					
antipyrine	•	•				
ASA	•	•			• invertebrates	• invertebrate
aureomycin						NEL antimicrobial effects
bacitracin					• invertebrates	
benzoic acid	•					
benzaldehyde	•				• chick teratogenicity	
benzylpenicillin						• algal growth
betaxolol	•	•				
bezafibrate	•	•				
biphenylol	•	•				
bisoprolol	•	•				
bisphenol	•					• rat repro
bleomycin	•	sw/dw				

Pharmaceutical Chemical Ingredient	Environmental Detection				Toxicity (aquatic)	
	ww	sw (gw,dw)	sed/sldg	biota	acute	subchronic
bromocyclen					• algae, invertebrates	
caffeine	•	•				
carazol	•	•				
carbamazepin	•	•				
chlomadinone acetate	•					
chloramphenicol	•	•			• sed. bacteria	
chlorophene	•	•				
chloroxylenol	•	•				
chlorotetracycline			soil		• terrestrial effects; algae	
ciprofloxacin	•	•			• bacteria, algae, invertebrates, fish	
cisplatin					• genotox	
clarithromycin	•	•				
clenbuterol	•	•				
clofibrate	•	sw; dw			• bacteria, algae, invertebrates, fish	
corticosterone					• estrogenic effects in quail	
cyclophosphamide	•					• carcinogenicity/mutagenicity
dehydroisoandrosterone	•					
dextropropoxyphene		•				
diatrozoate		•				
diazepam	•	sw/gw/dw			• invertebrate	
DES					• algae, invertebrates, fish	
diclofenac	•	sw/gw				
digoxin					• invertebrate	
dimethisterone	•					
DPTA		•			• bacteria, algae, invertebrates, fish	• invertebrate
EDTA		•			• bacteria, invertebrates, fish	• invertebrate; algae; rat
erythromycin	•	•				

Pharmaceutical Chemical Ingredient	Environmental Detection				Toxicity (aquatic)	
	ww	sw (gw,dw)	sed/sldg	biota	acute	subchronic
estradiol	•	•			• estrogenic effects in fish; quail	
estradiol-17B	•	•				
estriol	•					
estrogen	•	•	chicken manure		• invertebrates	• plants
estrone	•	•				• estrogenic effects in fish
ethinyl estradiol	•	•			• algae, invertebrates, fish; quail	• estrogenic effects in fish; invertebrates
ethynodiol diacetate	•					
etiocholanolone	•					
fenfluramine hydrchloride					• reproduction invertebrates	
fenofibrate	•	sw/gw				
fenoprofen	•	•				
fenoterol	•	•				
flumequine (aquaculture use)	•				• bacteria, invertebrate	phytotoxicity
fluoxetine					• reproduction and behavior invertebrates	
fluvoxamine					• reproduction invertebrates	
furazolidone					• bacteria, algae, invertebrates, fish	
gemfibrozil	•	•				
hydroquinone					• bacteria, algae, invertebrates, fish, cat , dog, guinea pig, insect, rabbit, rat, mouse, pigeon	• rat, plant
ibuprofen	•	sw/gw			• bacteria, algae, invertebrates, fish	
ifosamide	•					
indomethacin	•	•				
iopamidol	•					
iopromide	•	•			• bacteria, algae, invertebrates, fish	• invertebrate

Pharmaceutical Chemical Ingredient	Environmental Detection				Toxicity (aquatic)	
	ww	sw (gw;dw)	sed/sldg	biota	acute	subchronic
ivermectin		•	Feces; soil		• invertebrates, fish,; terrestrial insect, bird, plants, bacteria	• terrestrial invertebrate, bird
kanamycin					• bacterial resistance	
ketoprofen	•	•				
medroxyprogesterone	•					
meprobamate		gw				
mestranol	•					
methaqualone	•					
methotrexate	•				• bacteria, algae, invertebrate, fish	
metoprolol	•	•				
metronidazole	•	•			• algae, invertebrate	• invertebrate
mitomycin					• genotoxicity bacteria	
moxestrol					• estrogenic effects terrestrial bird	
nadolol	•	•				
naproxen	•	•				
nicotine	•					
neomycin						Antibiotic rest
n-methylphenacetin		sw/gw				
nerol					• terrestrial birds	
nitrofurantoin					• genotoxicity	
nitrofurazone					• algae, invertebrate • genotoxicity	
nonylphenol ethoxylate	•					• fish
norepinephrine					• invertebrate	
norethindrone	•					
norethindrone acetate	•					
norethisterone	•	•				
norethynodrel	•					
novobicin					• bacteria	Antibiotic resistance

Pharmaceutical Chemical Ingredient	Environmental Detection				Toxicity (aquatic)	
	ww	sw (gw,dw)	sed/sldg	biota	acute	subchronic
octylphenol						• subchronic terrestrial rat
ofloxacin	•	•			• genotoxicity	
olaquindox					• algae, invertebrate	• invertebrate
oxolinic acid					• bacteria, invertebrate	• invertebrate
oxytetracycline			•		• bacteria, invertebrate; terrestrial plant	• invertebrate
paroxetine					• reproduction invertebrates	
penicillin		dw				
pentoxifylin	•	•				
phenazone		sw, gw				
phenobarbital		gw				
phenobarbitone					MFO induction?	
phensuximide		gw				
phenylpropionic acid	•					
phenylsalicylate	•					
pivmecillinam					• bacteria, algae, invertebrates, fish	
platinum	•					
pregnanediol	•					
progesterone	•					
propanolol	•	•			• invertebrate	
propanoprolol	•	•				
propiphenazone	•	sw/gw				
propylphenazone		sw/gw				
roxithromycin	•	•				
saccharin	•					
salbutamol	•	•				
salicylic acid	•	•			• bacteria, algae, ciliates, invertebrate, fish	
serotonin					• invertebrates	

Pharmaceutical Chemical Ingredient	Environmental Detection				Toxicity (aquatic)	
	ww	sw (gw,dw)	sed/sldg	biota	acute	subchronic
spiramycin					• algal growth	
streptomycin					• bacteria, algae, invertebrate	• invertebrate
sulfadiazine					• invertebrate	• invertebrate
sulfadimethoxine					• invertebrate; plant	
sulfamethoxazole	•	sw,gw				
sulfonamides		gw; leachate				
terbutaline	•	•				
testosterone	•				• estrogenic effects terrestrial bird	
tetrabromo-o-cresol	•	•				
tetracycline		•			• algae, invertebrate	• invertebrate
theophylline		•				
timolol	•	•				
tolfenamic acid	•					
triclosan		•				
trimethoprim	•	•			• bacteria, algae, invertebrate, fish	
tylosin					• algae, invertebrate	• invertebrate
Verapamil					• increases toxicity of other drugs to aquatic organisms	

Total No. Pharmaceuticals Detected in Environmental Samples = 107; Effect data identified for No. Pharmaceutical = 68; Env. Conc. Data and Effects data for No. Pharmaceuticals = 28

* assumed to be lipophilic d.t. detection in breast milk.

Table 3b: Overview of Environmental Monitoring and Effects Data Reviewed – Cosmetic and Personal Care Products

Table 3b: Overview of Environmental Monitoring and Effects Data Reviewed – Cosmetic and Personal Care Products

Cosmetic Personal Care Product Ingredient	Environmental Detection				Toxicity (aquatic)	
	ww	sw (gw/dw)	sed/sldg	biota	acute	chronic
Musks:						
AETT –synthetic musk						rat neurotoxicity
ADBI – Celestolide	•	•	•	•	Genotoxicity/mutagenicity	
AHMI -Phantolid				•	Genotoxicity/mutagenicity	
AHTN – Tonalid	•	•	•	•	• algae Genotoxicity/mutagenicity	• aquatic invertebrate, fish, terrest invertebrates ; rat
ATII – Traseolide				•	Genotoxicity/mutagenicity	
HHCB – Galaxolide	•	•	•	•	• algae Genotoxicity/mutagenicity	• aquatic invertebrate, fish, terrest invertebrates ; rat
musk ketone	•	•	•	•	• bacteria, algae, invertebrate	• aquatic invertebrate, fish, terrest invertebrates ; rat
musk xylene	•	•	•	•	• bacteria, algae, invertebrate, fish mutagenicity	• aquatic invertebrate, fish, terrest invertebrates ; rat • mice carcinogenicity
musk moskene	•	•				
4-tert-octylphenol	•		sludge			• teratogenicity - chicks
benzaldehyde	•					
benzoic acid	•					
biphenylol	•	•				
EDTA		•			• bacteria, algae, invertebrate, fish	• algae; invertebrates; rat
LAB		•	•		• bacteria, algae, invertebrate, fish	• invertebrate

Cosmetic Personal Care Product Ingredient	Environmental Detection				Toxicity (aquatic)	
	ww	sw (gw/dw)	sed/sldg	biota	acute	chronic
MEA					• algae, invertebrates, fish	•
MIPA					• fish	
4-nonylphenol	•					• invert; fish
nonylphenol ethoxylates	•	•	•	•		
phenylpropionic acid		gw				
TEA					• invertebrate, fish	• algae, invertebrate
tetrabromo-o-cresol	•	•				
triclosan		•				
Total No. of Cosmetic and Personal Care Product Ingredients Detected in Environmental Samples = 19 Effect data identified for No. Cosmetics and P.C ingredients= 15; Env. Conc. Data and Effects data for No. Cosmetics and P.C ingredients = 11						
Food Additives						
Olestra	•				• algae; invertebrates; fish; sludge amended soils; primary; secondary treatment	• pigs; rodents; dogs; plants; soil microorganisms; teratogenicity; soil invertebrates
Saccharin	•					
caffeine	•	•				

Table 4: Parent Chemical Information

Table 4: Parent Chemical Information

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
(-)-limonene						flavour additive		
(+)-limonene								
[R,R]-EDDS	[S,S]-ethylene diamine disuccinate					chelator in cosmetics	pulp and paper, textile, metal, photographic, leather and detergent	Jaworska et al, 1999
[S,S]-EDDS							biodegradable chelator used in detergent applications	
16a-hydroxyestrone			not in TPP	hormone - estrogen				
2,4,6-tribromophenol		118-79-6		wound cleaning?				
4-chloro-m-cresol		59-50-7					disinfectant, cleaning of instruments, surfaces	Temes, Stumpf et al, 1998
4-chloroxylenol		88-04-0	774	vet/human medicated shampoo, liniment	76	disinfectant, cleaning surfaces	disinfectant,cleaning of surfaces	
4-nonylphenol						personal care?		
4-tert-octylphenol						cosmetics	other products	

Parent	*Parent Long Name*	*CAS No.*	*TPP Ingred. Code*	*Uses - Health*	*# Health Products*	*Uses - Personal Care*	*Uses - Other*	*Reference*
5,5-diallylbarbituric acid			not in TPP	barbiturate - used 1940s-1970s				
5-bromosalicylic acid		89-55-4				antiseptic		Temes, Stumpf et al, 1998
5-chlorosalicylic acid		321-14-2						
5-fluoracil			not in TPP	cytotoxic drug; antineoplastic agent inhibits DNA synthesis and RNA process				
acetaminophen		103-90-2	270	NSAID; analgesic	37			
actinomycin D				antibiotic				
alkylphenols						presonal care	industrial detergent	
allura red							synthetic food colorant	Chen et al. 1998
aluminum			various	ingredient on OTC drugs (eg. Antacids, topical pharmaceuticals-antiperspirants)	29	ingredient in cosmetics (lipsticks)		
amaranth	trisodium salt of 1-(4-sulpho-1-naphthylazo)-2-naphthol-3,6-disulphonic acid)			pharmaceutical colourant				Brain et al. 1971

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
amitriptyline			10187	antidepressant	36			
amlodipine		88150-42-9	11344	cardiac drug - Ca channel blocker	2			
amoxicillin			11101	antibiotic - vet/human	64			
					64			
ampicillin			8450	antibiotic	36			
					36			
amprolium			6458	antiprotozoal - vet	2			
androsterone			not in TPP	natural hormone				
antipyrine		60-80-0	8859	NSAID	6			
ASA	acetylsalicylic acid		150	NSAID; analgesic	14			Temes, Stumpf et al, 1998
		50-78-2			14			
		487-54-7			14			
					14			
					14			
		490-79-9			14			
					14			

Parent	*Parent Long Name*	*CAS No.*	*TPP Ingred. Code*	*Uses - Health*	*# Health Products*	*Uses - Personal Care*	*Uses - Other*	*Reference*
ASA	acetylsalicylic acid	69-72-7	150	NSAID; analgesic	14			Temes, Stumpf et al, 1998
aureomycin			not in TPP	antibiotic - vet				
bacampicillin			8350	antibiotic	1			
bacitracin			8502	antibiotic - vet/human	27			
bambermycin			not in TPP	antibiotic - vet				
bendroflumethiazide		73-48-3		diuretic				
benzaldehyde						preservative	preservative	
benzoic acid						personal care?		
benzylpenicillin			not in TPP	antibiotic				
betaxolol		63659-18-7	11219	anti-hypertensive - beta blocker; antiglaucoma	2			
bezafibrate		41859-67-0	949	antilipemic	3			
biphenylol		90-43-7				cleaning hands	cleaning of surfaces, instruments, laundry	Temes, Stumpf et al, 1998
bisoprolol		66722-44-9	1218	Betablocker	2			Stan and Heberer, 1997; Hirsch et al. 1996
bisphenol						personal care?		

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
bisphenol-A						component of dental resin		Ansar Ahmed, 2000
bleomycin			1148	antineoplastic	2			
brilliant blue							synthetic food colorant	Chen et al. 1998
bromocyclen			not in TPP	antiparasitic agent - vet				
bromophene		15435-29-7		antiseptic; cleaning wounds		cleaning skin	disinfectant; cleaning of instruments	Temes, Stumpf et al, 1998
budesonide		51333-22-3	7581	anti-asthmatic - adrenals, antiinflammatory	12			
caffeine			9358	stimulant/opiate agonist; methyl xanthine	98	coffee, tea, soft drinks, chocolate	coffee, tea, soft drinks, chocolate	
caffeine citrate			9357		16			
carazol		57775-28-8	not in TPP	Betablocker				Stan and Heberer, 1997; Hirsch et al. 1996
carbamazepin				antiepileptic drug/ antidepressant; for partial seizures; bipolar depression; trigeminal neuralgia				
cefotiam dihydrochloride				antiblotic				

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
ceftiofur sodium			1126	antibiotic - vet	2			
cephalexin			8376	antibiotic	26			
chlormadinone acetate			not in TPP	drug?				
chloramphenicol			8579	antibiotic - vet/human	33			
					33			
chlordiazepoxide			10260	sedative-hypnotic; anxiolytic agent; muscle relaxant	16			
chlorhexidine			various forms in TPP	antiseptic				
chlorhexidine acetate			5280		28			
chlorhexidine gluconate			626	disinfectant	80			
chlormadinone acetate	6-chloro-17-hydroxy-pren-4,6-diene-3,20-dione		not in TPP	synthetic progestin				
chlorophene		120-32-1	7044	antiseptic	2	cleaning skin, hands	cleaning of instruments, surfaces	Temes, Stumpf et al, 1998
chloroxylenol		88-04-1	774	antiseptic	76			
chlortetracycline			8668	antibiotic - vet	4			
chlortetracycline hydrochloride			8671		15			

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
cholesterol						personal care?		
CI Pigment 57:1		5281-04-9				colouring agent in cosmetics(60% of use in Denmark)	food additive in EU	Moller and Wallin, 2000
CI Pigment Orange 5		3468-63-1				possible colouring agent in cosmetics	paint (50% in Denmark)	
CI Pigment Red 2		6041-94-7					Printing ink (90% in Denmark)	
CI Pigment Red 23		6471-49-4					Printing ink (99% in Denmark)	
CI Pigment Red 3		2425-85-6					paint (80% in Denmark)	
CI Pigment Red 4		2814-77-9					paint (90% in Denmark)	
CI Pigment Red 53:1		5160-02-1					paint (80% in Denmark)	
CI Pigment Red 64:1		6371-76-2					not registered	
CI Solvent Orange 7								
CI Solvent Yellow 14	1-phenylazo-2-hydroxynaphthalene	842-07-9					miscellaneous	
CI Solvent Yellow 7		3118-97-6						
cinnamaldehyde						flavour additive		

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
cinnamyl alcohol						flavour additive		
ciprofloxacin			93	antibiotic; quinolone;in animal feed	9			
					9			
cisplatin			not in TPP	antineoplastic				
citalopram		59729-33-8	11847	antiepileptic drug	2			
citral						flavour additive		
citronellal								
clarithromycin			8318	antibiotic	4			
clenbuterol		37148-27-9	1920	beta-2-sympathomimetic - bronchodilator	2			
clindamycin			8551	antibiotic - vet/human	18			
clofibrate			9842	antilipemic; lipid lowering drug	2			
		882-09-7			2			
					2			
		637-07-0			2			
cloxacillin			8375	antibiotic	18			

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
codeine			phosphate and sulphate in TPP	opiate analgesic				
codeine phosphate			9131		12			
codeine sulfate			6750		10			
colchicine			6760	NSAID; antiinflammatory drug used in gouty arthritis; alkaloid from autumn crocus	21			
corticosterone			not in TPP	hormone; adrenal steroid				Robinson and Verrinder Gibbins, 1984
croton aldehyde						flavour additive		
cyclophosphamide		50-18-0	5927	antineoplastic	12			
danofloxacin	1-cyclopropyl-6-fluoro-7-(1S,4S-5-methyl-2,5-diazabicyclo[2.2.1] heptan-2-yl)-1,4-dihydro-4-oxoquinoline-3-carboxylic acid		not in TPP	antibiotic				
DEA		111-42-2				cosmetics and toiletries	surfactants, metal working fluids, textile chemicals, gas conditioning chemicals, agricultural chemical intermediates, cement grinding aids	Davis and Carpenter, 1997

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
decamethonium			not in TPP	neuromuscular depolarizing blocking agent/hypertension drug (block aceytl choline at nicotinic receptors)				
dehydroisoandrostero ne				natural hormone				
demethylchlortetracylc ine			8664	antibiotic	2			
desogestrel		54024-22-5	660	sex hormone	4			
dextropropoxyphene			9952	opiate analgesic	4			
dextropropoxyphene napsylate			2555	opiate agonist	1			
diatrozoate			two forms in TPP	x-ray contrast medium				
diatrozoate meglumine			10131		13			
diatrozoate sodium		737-31-5	10133		8			
diazepam		439-14-5	9418	sedative-hypnotic (anxiolytic agent); claming effect, drowsiness	21			
diclofenac		15307-79-6	2013	NSAID	50			
dicloxacillin			not in TPP	antibiotic				

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
dicloxacillin			not in TPP	antibiotic				
diethylstilbesterol				hormone				
digoxin		20830-75-5	6731	cardiac glycoside	11			
digoxin immune fab (ovine)			7676		1			
dimethicone			433	antacid	46			
dimethisterone	6A,21-dimethyl-17-hydroxy-pregn-4-en-17-diol		not in TPP	hormone; synthetic progestin				
dimethyl octanol						flavour additive		
doxycycline			8642	antibiotic	16			
DPMI	6,7-dihydro-1,1,2,3,3-pentamethyl-4(5H)indanone	33704-61-9				fragrance in personal care products	fragrance in household products	Rimkus, 1999
DPTA	diethylenetriaminepentaacetic acid		not in TPP	chelator for metal poisoning			pulp and paper industry	Sillanpa, 1997
EDTA	ethylenediaminetetraacetic acid		2243	chelator	2	chelator used in cosmetic industry	metal, rubber, leather, photographic, textile, pulp and paper and food industries	
efrotomycin			not in TPP	antibiotic - vet				

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
ellipticine			not in TPP	?				
enalapril		75847-73-3	1810	anti-hypertensive agent; ACE inhibitor, human/vet - cardiac drug, diuretic, vasodilator (vet)	18			
enrofloxacin			8328	antibiotic - vet	7			
					7			
ephedrine			various forms in TPP	antihistamine				
ephedrine (racemic)			3718		12			
ephedrine hydrochloride			3714		15			
ephedrine sulfate			8937		5			
erythromycin			8618	antibiotic	55			
erythromycin lactobionate			8613		2			
erythromycin stearate			8612		4			
estradiol		50-28-2	7419	sex hormone, human/vet	8			
estradiol-17B			94	sex hormone, human	16			

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
estradiol benzoate			7423	sex hormone, human/vet	11			
estradiol deinanthate			7411	sex hormone, human	1			
estradiol enanthate			7417	sex hormone, vet	2			
estradiol valerate			7420	sex hormone, human	4			
estradiol-17-B-cypionate			7424	sex hormone, vet	3			
estriol				natural hormone				
estrogen		56-53-1	7440	sex hormone	27			
estrogens (conjugated)					27			
estrogens (esterified)			7436		3			
estrone			7445	natural hormone	10			
ethinyl estradiol		57-63-6	7426	sex hormone, human/vet	66			
ethynodiol diacetate			7410	synthetic hormone	4			
etiocholanolone			not in TPP	natural hormone				
farnesal						flavour additive		
farnesol								

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
fatty acids - branched chains						presonal care		
fatty acids - normal chains								
fatty acids - unsaturated acids								
fenfluramine hydrochloride			not in TPP	SSRI; antidepressant/anti epileptic; serotonin agonist (releaser)				
fenofibrate		42017-89-0	1381	antilipemic	12			
		49652-28-9			12			
fenoprofen		31879-05-7	11356	NSAID	2			
fenoterol			2252	cardiovascular drug; heart/asthma treatment; beta-agonist; beta-2-sympathomimetic - bronchodilator	5			
flavour compounds						flavour additives		
florfenicol			63	antibiotic - vet; used in fish farms	2			
flumequine			not in TPP	antibiotic - vet; quinolone; animal feed				
fluoxetine		54910-89-3	11130	antidepressant/ antiepileptic (SSRI)	32			

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
fluvoxamine		54739-18-3	1212	antidepressant / antidepressant (SSRI)	20			
fragrance compounds						fragrance additives		
furazolidone			10161	antibiotic - vet; used in fish farms; chickens	2			
furosemide		54-31-9	10091	diuretic	23			
gemfibrozil		25812-30-0	1094	antilipemic	20			
geraniol						flavour additive		
gestodene		60282-87-3	not in TPP - progesterone	sex hormone				
hexachlorophene	[2,2'methylene bis(3,4,6-trochlorophenol)]		9751	topical antiseptic	1			
hycanthone			not in TPP	antiparasitic agent - antischistososmal				
hydrochlorothiazide			10234	diuretic	63			
hydrogen peroxide			7128	antiseptic human/vet	50	mouthwashes, gargles	laundry bleach	
hydrogen peroxide (urea)			3991	antiinfective human/vet	2			

Parent	*Parent Long Name*	*CAS No.*	*TPP Ingred. Code*	*Uses - Health*	*# Health Products*	*Uses - Personal Care*	*Uses - Other*	*Reference*
hydroquinone	1,4-dihydroxybenzene	123-31-9	4439	skin lightening cream	39	principally used in hair dyes and colours; also used inlipsticks, skin fresheners and other skin care products		
hydroxy-citronellal						flavour additive		
ibuprofen	2-(4-isobutylphenyl)propionic acid	15687-27-1	2609	NSAID; analgesic	38			
ifosamide		3778-73-2	not in TPP	antineoplastic				
indigo carmine							synthetic food colorant	Chen et al. 1998
indomethacin		53-86-1	10126	NSAID	25			
iohexol		66108-96-0	8092	x-ray contrast media	4			
iopamidol		60166-93-0	8042		3			
iopromide	[N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino-N-methyl-1,3-benzenedicarboxamide		521		3			
		73334-07-3			3			
iotrolan			not in TPP	x-ray contrast agent?				

Parent	*Parent Long Name*	*CAS No.*	*TPP Ingred. Code*	*Uses - Health*	*# Health Products*	*Uses - Personal Care*	*Uses - Other*	*Reference*
ivermectin	22,23-dihydroavermectin B1		623	antiparasitic vet drug	22			Bloom and Matheson, 1993
					22			
					22			
kanamycin			not in TPP	antibiotic				
keloprofen				pharmaceutical				AWWR, 1995 cited in Stan and Heberer, 1997
ketoconazole		65277-42-1	1855	topical antifungal	6			
ketoprofen		22071-15-4	2327	NSAID (vet, human)	40			
LAB	linear alkyl benzene					intermediate used in detergent industry 0.5% unreacted product in LAS		Binetti et al. 2000
lactic acid producing organisms			11532	anti-diahrrea	1			
L-ephedrine hydrochloride			8944	antihistamine	11			
levodopa			4068	CNS agent; neurotransmitter; antiparkinson drug	19			
levonorgestrel			7490	synthetic hormone	11			
L-menthol			418	plaster, nasal ointment	3			

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
lynoestrenol			not in TPP	synthetic hormone				
malachite green			9741	antimicrobial agent - used in fish nurseries	2			
MEA	monoethanloamine	141-43-5				cosmetics and toiletries	surfactants, metal working fluids, textile chemicias, gas conditioning chemicals, agricultural chemical intermediates, cement grinding aids	Davis and Carpenter, 1997
mebendazole			2434	antihelminthic fish, vet, human	6			
meclofenamic acid		644-62-2	2114	NSAID (vet)	1			Temes, Stumpf et al, 1998
medroxyprogesterone acetate	17-hydroxy-6A-methyl-pregn-4-ene-3;20-dione, acetate		7538	hormone; synthetic progestin	22			
mefenamic acid			10002	NSAID	6			
menthol			265	lip balm, liniment, cough medicine, cold medicine	30			
meprobamate			10233	opiate agonist; sedative-hypnotic barbiturate	6			
meropenem			43254	antibiotic	2			

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
mestranol	ethynyl estradiol-3metyl ether		7429	synthetic estrogen	4			
methaqualone			not in TPP					
methicillin				antibiotic				
methotrexate	4-amino-10-methyl folic acid	59-05-2	5900	antineoplastic	11			
methyldopa			10295	antihypertensive agent, diuretic	23			
methyltestosterone			7497	hormone - vet/human	4			
metoprolol		56392-17-7	2167	Betablocker	33			Hirsch et al. 1996
metronidazole			9880	antiprotozoal; antifungal	17			
minocycline			11182	antibiotic	21			
					21			
MIPA	monoisopropanolamine	78-96-6				cosmetics and toiletries	surfactants, metal working fluids, textile chemicias, gas conditioning chemicals, agricultural chemical intermediates, cement grinding aids	Davis and Carpenter, 1997
mitomycin			2195	antineoplastic	6			

Parent	*Parent Long Name*	*CAS No.*	*TPP Ingred. Code*	*Uses - Health*	*# Health Products*	*Uses - Personal Care*	*Uses - Other*	*Reference*
monensin			8558	antibiotic - vet	6			
moxestrol	11B-methoxy ethynyl estradiol			ethynyl estradiol analogue				Robinson and Verrinder Gibbins, 1984
moxidectin			225	antiparasitic - vet	6			
musk - AHMI (phantolid)	acetyl hexamethyl indan		not in TPP	pharmaceutical		fragrance ingredient - possible replacement for AETT		Gressel et al. 1980
musk -ADBI (Celestolide)	4-acetyl-1,1-dimethyl-6-tert-butyldihydroindene;acetyl tertiary butyl dimethyl indan	13171-02-1				fragrance - polycyclic musk; possible replacement for AETT	fragrance in household products	Rimkus, 1999; Gressel et al. 1980
musk -AETT	acetyl ethyl tetramethyl tetralin					synthetic musk - previously used as fragrant compound		Cammer, 1980
musk -AHDI (Phantolide)	6-acetyl-1,1,2,3,3,5-hexamethyldihydroindene	15323-35-0				fragrance - polycyclic musk	fragrance in household products	Rimkus, 1999
musk -AHTN (Tonalid)	7-acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene ; acetyl methyl tetramethyl tetralin					fragrance - polycyclic musk replacement for AETT	fragrance in laundry dertergent, air freshener, fabric softener, household lceaning products	Balk and Ford, 1999, Rimkus, 1999
		1506-02-1; 21145-77-7						

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
musk -ATII (Traseolide)	4-acetyl-1,1,2,6-tetramethyl-3-isopropyldihydroinden e	33704-61-9				polycyclic musk; fragrance in personal care products	fragrance in household products	Rimkus, 1999
musk -ATTN (Versalide)	7-acetyl-1,1,4,4-tetramethyl-6-ethyltetrahydronaphth alene	88-29-9						
musk -cashmeran (DPMI)	6,7-Dihydro-1,1,2,3,3-pentamethyl-4(5H)indanone	33704-61-9				fragrance ingredient (synthetic musk) used in perfumes, lotions, detergents	food additives, cigarettes, fish baits	
musk -celestolide (ADBI)	4-acetyl-1,1-dimethyl-6-tert.butyldihydroindene	13171-00-1						Gressel et al. 1980
musk -HHCB (Galaxolide)	1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta -gamma-2-benzopyran	1222-05-5				fragrance - polycyclic musk	fragrance in laundry dertergent, air freshener, fabric softener, household iceaning products	Balk and Ford, 1999; Rimkus, 1999; Gressel et al. 1980
musk nitro - ambrette		83-66-9				fragrance - nitro musk	fragrance in household cleaning products	

Parent	*Parent Long Name*	*CAS No.*	*TPP Ingred. Code*	*Uses - Health*	*# Health Products*	*Uses - Personal Care*	*Uses - Other*	*Reference*
musk nitro - ketone						fragrance - nitro musk	fragrance in household cleaning products	Tas, Balk et al, 1997
		81-14-1						
musk nitro - moskene		116-66-5						
musk nitro - tibetene		145-39-1						
musk nitro - xylene								Tas, Balk et al, 1997
		81-15-2						
nadolol		42200-33-9	2099	anti-hypertensive - beta blocker	14			
nafcillin			not in TPP	antibiotic				
naproxen		22204-53-1	2414	NSAID	46			Temes, Stumpf et al, 1998
neomycin			8638	antibiotic - vet/human	98			
nerol						flavour additive		

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
nerol						flavour additive		
new red							synthetic food colorant	Chen et al. 1998
nicotinamide			not in TPP					
nicotine			4365	smoking cessation aid	20		tobacco component	
nitrazepam		146-22-5	9558	sedative-hypnotic	6			
nitro musk						fragrance		
nitrofurantoin			10196	antimicrobial - vet/human; used in fish farms	11			
nitrofurazone			6805	antimicrobial- vet; used in fish farming; chicken	53			
N-Methylphenacetin			not in TPP	pharmaceutical				Stan and Heberer, 1997
nodolol								
nonylphenol diethoxylate						cosmetics	other products	
nonylphenol ethoxylates			10217	spermicide	1	surfactants used in cosmetics, detergents, spermicide, cleaning agent		

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
nonylphenol/alkylphenols				spermicide		presonal care	industrial detergent	
norepinephrine			7393	sympathomimentic (adrenergic) agent	1			
norethindrone	17-hydroxy-19-no-17A-pregn-4-en-20-yn-3-one		7500	hormone; synthetic progestin	21			
norethindrone acetate			7498		9			
norethisterone			not in TPP	hormone				
norethynodrel	17-hydroxy-19-no-17A-pregn-5(10)-en-20-yn-3-one			hormone; synthetic progestin				
norfloxacin	1-ethyl-6-fluoro-7-piperazin-1-yl-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid		1838	antibiotic	6			
norgestrel			7503	hormone; synthetic hormone	2			
novobicin			not in TPP	antibiotic - vet				
octanal						flavour additive		
octylphenol								
ofloxacin			954	antibiotic	7			

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
olaquindox			not in TPP	antibiotic				
olestra							noncaloric fat replacer in foods	Allgood et al. 1997
oral contraceptive			various	hormone				
oxacillin			not in TPP	antibiotic				
oxolinic acid				antibiotic - vet; quinolone				
oxytetracycline			8652	vet antibiotic - used in fish nurseries	17			
oxytetracycline hydrochloride			8651	antibiotic - vet	38			
p-aminobenzoic acid			not in TPP			sunscreen active ingredient		Shaw et al. 1992 cited in Stevenson and Davies, 1999
paratect	morantel tartrate			anthelmintic - veterinary				
paroxetine		61869-08-7	11340	anti-depressant (SSRI)	3			
PBSA	2-phenylbenzimidazole-5-sulfonic acid		11975	sunscreen agent	32	common sunscreen constituent		Stevenson and Davies, 1999

Parent	*Parent Long Name*	*CAS No.*	*TPP Ingred. Code*	*Uses - Health*	*# Health Products*	*Uses - Personal Care*	*Uses - Other*	*Reference*
PBZ	2-phenylbenzimidazole		not in TPP					Stevenson and Davies, 1999
penicillin			various forms in TPP	antibiotic				
penicillin G				antibiotic vet/human				
penicillin G benzathine			11521	antibiotic - vet/human	7			
penicillin G potassium			8439		15			
penicillin G procaine			8433		34			
penicillin G sodium			8435	antibiotic	6			
penicillin V			8428		15			
					15			
pentobarbital			8228	sedative; barbiturate - vet/human	8			
pentoxifylin			not in TPP	drug?				
phenacetin				NSAID; analgesic				
phenazone				pharmaceutical				Stan and Heberer, 1997

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
phenobarbital			8280	sedative; antiepileptic; barbiturate seizure control	2			
phenobarbitone			8282	barbiturate	25			
phenol			6935	antiseptic ingredient in OTC drugs; dental products, cold sore/canker products, skin care for dandruff and seborrhoea, topical first aid products, cough, cold, sore throut and allergy products	57			
phensuximide			not in TPP	anti absence drug; anti-epileptic drug				
phenylbutazone	1,2-diphenyl-4-n-butyl-3,5-dioxopyrazolidine		9536	NSAID - vet/human treat gout, arthritis and musculoskeletal disorders	30			
					30			
					30			
					30			
					30			
					30			

Parent	*Parent Long Name*	*CAS No.*	*TPP Ingred. Code*	*Uses - Health*	*# Health Products*	*Uses - Personal Care*	*Uses - Other*	*Reference*
phenylbutazone	1,2-diphenyl-4-n-butyl-3,5-dioxopyrazolidine		9536	NSAID - vet/human treat gout, arthritis and musculoskeletal disorders	30			
phenylpropanolamine			8843	antihistamine	61			
phenylpropionic acid			not in TPP					
phenylsalicylate		118-55-8				antiseptic	ingredient in laquers, adhesives, waxes, polishes, manuf of polymers	Temes, Stumpf et al, 1998
piperazine			10006	antihelminthic-vet/human	14			
piperazine adipate			9431	antihelminthic - vet/human	6			
piperazine citrate			7153	antihelminthic - human	1			
piperazine hydrochloride			10070	antihelminthic - vet	6			
piperazine phosphate			5970		2			
pivampicillin			8347	antibiotic	2			
pivmecillinam			8343	antibiotic; beta-lactam antibiotic				

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
platinum			699	ingredient in antineoplastic drugs and homeopathic products	18			
ponceau 4R							synthetic food colorant	Chen et al. 1998
potassium chloride			53	mineral supplements, dialysis, replacement preps, various drugs	43			
potassium chloride (chloride)			11393	mineral supplements	21			
potassium chloride (chlorine)			4608	mineral supplements, disinfectants	57			
potassium chloride (potassium)			6485	mineral supplements, replacement preps, disinfectants	52			
pregnanediol			not in TPP	natural hormone				
progesterone			7554		12			
promethazine			7952	antihistamine	9			
propanolol			not in TPP	anti-hypertensive - beta blocker				
		525-66-6						

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
propanoprolol		3506-09-0	not in TPP	Betablocker				Hirsch et al. 1996
propiphenazone				pharmaceutical				Stan and Heberer, 1997
propylphenazone	1,2-dihydro-1,5-dimethyl-4-(1-methylmethyl)-2-phenyl-3H-pyrazol-3-one	479-92-5		NSAID				
pseudoephedrine hydrochloride			6492	decongestant; antihistamine	19			
pseudoephedrine sulphate			8942		9			
puromycin			not in TPP	inhibits protein synthesis in animal and other cells. Antiviral				
putative genotoxic agents - direct acting								
quinolone antibiotics				antibiotic - general class - vet/human				
receiving waters of sewage effluents								
recombinant DNA fermentations	recombinant proteins using E.coli K-12							Kane. 1993
riboflavin-5-phosphate			5020	vitamin - vet/human	10			
riboflavin-5'-phosphate sodium			5021		20			

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
roxithromycin			not in TPP	antibiotic				
saccharin							sweetener	
salbutamol		18559-94-9	2585	Beta-selective agonist;vasodilator; relax smooth muscle; cardiac drugs;bronchodilators/inhalers	56			
salicylic acid			9766	vet skin cleanser, face cleanser, keratolytic, dermatic	19		food preservative	Temes, Stumpf et al, 1998
sarafloxacin			not in TPP	antibiotic - vet; quinolone; used in chickens				
serotonin	5-hydroxytryptamine			neurotransmitter				
sewage treatment effluents								
sodium lauryl sulphate						anionic surfactant used in cosmetics as cleansing agents		
spiramycin			8589	antibiotic	2			
spironolactone			7408	anithypertensive agent; diuretic	9			
					9			
streptomycin			8603	antibiotic - vet	14			

Parent	*Parent Long Name*	*CAS No.*	*TPP Ingred. Code*	*Uses - Health*	*# Health Products*	*Uses - Personal Care*	*Uses - Other*	*Reference*
sulfadiazine			8199	antibiotic	15			
sulfadimethoxine			8165	antibiotic - vet	2			
sulfadimidine			not in TPP					
sulfamethazine			8187	antibiotic - vet/human	33			
sulfamethazine sodium			8185	antibiotic - vet	23			
sulfamethoxazole			8174	antibiotic	25			
sulfanilamide			8207		12			
sulfasalazine			8138	antimicrobial agent; treat inflammatroy bowel disease	11			
sulfatrimethoprim			not in TPP	antibiotic - vet				
sulfonamides (various)				antibiotics - used 1940s-1970s				
Sunset Yellow FCF	disodium salt of 1-p-sulphophenylazo-2-naphthol-6-sulphonic acid			pharmaceutical colourant				Brain et al. 1971
tartrazine							synthetic food colorant	Chen et al. 1998

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
TEA	triethanolamine	102-71-6				cosmetics and toiletries	surfactants, metal working fluids, textile chemicias, gas conditioning chemicals, agricultural chemical intermediates, cement grinding aids	Davis and Carpenter, 1997
terbutaline		23031-25-6	2345	anti-asthmatic - sympathomimetic;beta-receptor agonist; adrenoreceptor agonist; bronchiodilator/inhalers	2			
testosterone			7485	hormone - vet/human	4			
testosterone cypionate			7487	hormone	3			
testosterone enanthanate			7486	hormone - vet/human	6			
testosterone propionate			7488		8			
testosterone undecanoate			7469	hormone	1			
tetrabromo-o-cresol		576-55-6				cleaning hands		Ternes, Stumpf et al, 1998
tetracycline			8652	antibiotic vet/human - used in fish ponds	49			

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
theobromine			9662	homeopathic; methyl xanthine; source cocoa; bronchodilator	1			
theophylline			231	respiratory smooth muscle relaxant; methylxanthine; source tea; bronchodilator treat asthma	37			
thiamine hydrochloride			5040	vitamin	20			
thiamine mononitrate			5038		82			
tiamulin			28	antibiotic - vet	6			
timolol		26839-75-8	2292	anti-hypertensive - beta blocker; use glaucoma	34			
tolbutamide			9563	sulfonylurea drug; treat hyperglycemia in non-insulin-dependent diabetics	4			
tolfenamic acid		13710-19-5	928	NSAID (vet)	4			Temes, Stumpf et al, 1998
tonalid	acetyl methyl tetramethyl tetralin					fragrance ingredient - possible replacement for AETT		Gressel et al. 1980

Parent	Parent Long Name	CAS No.	TPP Ingred. Code	Uses - Health	# Health Products	Uses - Personal Care	Uses - Other	Reference
triclosan		3380-34-5	2813	antiseptic - acne cream, hand soap	10	soap, toothpaste	odor eaters, in plastics for cutting boards, toys, kitchen utensils	
trimethoprim			8452	antibiotic - vet/human; dihydrifolate reductase inhibitor	42			
trimipramine			9906	diuretic	27			
tylosin			8591	antibiotic - vet	10			
verapamil		52-53-9	10110	cardiac drug - Ca ion influx inhibitor - anti-hypertensive	34			
warfarin			9054	anticoagulant	24		rodenticide	
xylometazolin		526-36-3	5869	alpha-agonist; nasal decongestant; OTC drugs	15			
zopiclone		146-22-5	1200	anti-hypertensive	9			

Table 5: Parent Chemical/ Breakdown Product Relationship

Table 5: Parent Chemical/Breakdown Product Relationship

Parent (short name)	*Parent (long name)*	*Breakdown Product*	*Breakdown Product (long name)*	*Relationship*	*Reference*
alkylphenols		alkylphenol-polyethoxylates (APE)		sewage biodegradation product	Purdom et al. 1994 cited in Crisp et al. 1998
amoxicillin		amoxicillin metabolites		metabolite	Hirsch et al, 1999
ampicillin		ampicillin metabolites		metabolite	Hirsch et al, 1999
ASA	acetylsalicylic acid	salicylic acid		metabolite	
		salicylic phenol glucuronide		metabolite	Fishbein and Flamm, 1972
		o-hydroxyhippuric acid		metabolite	
		salicyluric acid		metabolite	Fishbein and Flamm, 1972
		gentisic acid		metabolite	
		aminohippuric acid		metabolite	
		salicylic acid glucuronide		metabolite	Fishbein and Flamm, 1972
chloramphenicol		chloramphenicol glucuronides		metabolite	Hirsch et al, 1999
ciprofloxacin		ciprofloxacin metabolites		metabolite	Halling-Sorensen et al, 2000
clofibrate		clofibric acid derivative		metabolite	
		clofibric acid		metabolite (active)	Daughton and Ternes, 1999
		phenoxyalkanoic acid		metabolite	Buser et al. 1998a
dicloxacillin		dicloxacillin metabolites		metabolite	Hirsch et al, 1999

Parent (short name)	*Parent (long name)*	*Breakdown Product*	*Breakdown Product (long name)*	*Relationship*	*Reference*
diethylstilbesterol		diethylstilbesterol acetate		metabolite	Coats et al, 1976; Cited in Halling-Sorensen et al, 2000
enrofloxacin		enrofloxacin - phototransformation product		phototransformation product	
fenofibrate		fenofibric acid		metabolite (active)	Daughton and Ternes, 1999
iopromide	[N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-[(methoxyacetyl)amino-N-methyl-1,3-benzenedicarboxamide	iopromide metabolites		metabolites	
ivermectin	22,23-dihydroavermectin B1	ivermectin aglycone		metabolite	Halley et al, 1989
		ivermectin monosaccharide		metabolite	Halley et al, 1989
minocycline		minocycline metabolites		metabolite	Hirsch et al, 1999
musk -AHTN (Tonalid)	7-acetyl-1,1,3,4,4,6-hexamethyl-1,2;3,4 tetrahydronaphthalene; acetyl methyl tetramethyl tetralin	AHTN unidentified musk metabolites		metabolite	Balk and Ford, 1999
musk -HHCB (Galaxolide)	1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-gamma-2-benzopyran	HHCB-hydroxy acid		metabolite	Balk and Ford, 1999
		HHCB unidentified metabolite		metabolite	Balk and Ford, 1999
		HHCB-lactone		metabolite	Balk and Ford, 1999
musk nitro - ambrette		AMA (musk nitro metabolite)	1-tert-butyl-2,4-dimethyl-3-amino-6-methoxy-5-nitrobenzene	amino nitro metabolite	Berset et al. 2000
musk nitro - ketone		AMK (musk nitro metabolite)	4-acetyl-1-tert-butyl-3,5-dimethyl-2-nitro-6-aminobenzene	amino nitro metabolite	Berset et al. 2000
		musk - ketone derivatives		microbial transformation product	Daughton and Ternes, 1999
musk nitro - moskene		AMM (musk nitro metabolite)	1,1,3,3,5-pentamethyl-4-nitro-6-aminoindane	amino nitro metabolite	Berset et al. 2000

Parent (short name)	*Parent (long name)*	*Breakdown Product*	*Breakdown Product (long name)*	*Relationship*	*Reference*
musk nitro - tibetene		AMT (musk nitro metabolite)	1-tert-butyl-3,4,5-trimethyl-2-amino-6-nitrobenzene	amino nitro metabolite	Berset et al. 2000
musk nitro - xylene		musk nitro - xylene derivatives		microbial transformation product	Daughton and Ternes, 1999
		AMUXY (musk nitro metabolite)	1-tert-butyl-3,5-dimethyl-4-amino-2,6-dinitrobenzene	amino nitro metabolite	Berset et al. 2000
nicotinamide		nicotinic acid		hydrolysis product	Richardson and Bowron, 1985
nonylphenol/alkylphenols		nonylphenol		n/a	
oxacillin		oxacillin metabolites		metabolite	Hirsch et al, 1999
penicillin G		penicillin G metabolites		metabolite	Hirsch et al, 1999
penicillin V		penicillin V metabolites		metabolite	Hirsch et al, 1999
phenylbutazone	1,2-diphenyl-4-n-butyl-3,5-dioxopyrazolidine	oxyphenylbutazone		metabolite	Fishbein and Flamm, 1972
		n-caproyl hydrazobenzene		decomposition product	Fishbein and Flamm, 1972
		4-hydroxyphenylbutazone		photodegradation product	Fishbein and Flamm, 1972
		N-(2-carboxy-2-caproyl)-hydrazobenzene		photodegradation product	Fishbein and Flamm, 1972
		cis-azobenzene		photodegradation product	Fishbein and Flamm, 1972
		trans-azobenzene		photodegradation product	Fishbein and Flamm, 1972
propanolol		4-hydroxypropanolol		metabolite	Daughton and Ternes, 1999
spironolactone		canrenone		metabolite	Richardson and Bowron, 1985

Table 6: Summary of Absorption/ Metabolism/Excretion Data

Table 6: Summary of Absorption, Metabolism, Excretion Data

chemical	data type	descriptor	value	units	test matrix	method/parameters	reference
5-Fluoracil	metabolism	bile/plasma ratio	3.4			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
acetaminophen	metabolism	human	90% excreted as conjugates; 3-5% unmetabolized				Pfeiffer, 1977; Ellenhorn and Barceloux, 1988; Mutschler, 1991; McEvoy, 1992; Cited in Henschel et al, 1997
actinomycin D	metabolism	bile/plasma ratio	26.2			1 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
aluminum	absorption	human - GI tract	<1	%			Aluminum in Drugs by NDMAC and CCTFA, January 19, 2000.
	absorption	human - GI tract	0.2 to 1.5	%	estimated		Greger, 1993 cited in Aluminum in Drugs by NDMAC and CCTFA, January 19, 2000.
	excretion	human-feces	99.9	%	majority excreted in feces remainder in urine		Greger, 1993 cited in Aluminum in Drugs by NDMAC and CCTFA, January 19, 2000.
aminohippuric acid	metabolism	bile/plasma ratio	>2344			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
antipyrine	metabolism	bile/plasma ratio	5.9			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
ASA	metabolism	human	major metabolite is salicylic acid - 90% excreted in urine in conjugate and free forms				Parke, 1968 and Jurna, 1992; Cited in Heschel et al, 1997
benzoic acid	metabolism	bile/plasma ratio	1			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
chloramphenicol	metabolism	manure	glucuronide reactivated to parent				Berger et al, 1986;Cited in Halling-Sorensen et al, 2000
	metabolism	manure	reactivated in manure		excreted as glucuronide then reactivated to parent in manure		Berger et al, 1986; Cited in Halling-Sorensen et al, 1998
CI Pigment Red 53:1	uptake	oral absorption	none		rats		Leist 1982 cited in Moller and Wallin, 2000
CI Solvent Yellow 14	uptake	dermal absorption	57.6	%	hairless guinea pig		Collier et al. 1993 cited in Moller and Wallin, 2000
	uptake	dermal absorption	26.4	%	human		Collier et al. 1993 cited in Moller and Wallin, 2000
	uptake	dermal absorption	32.8	%	mice		Collier et al. 1993 cited in Moller and Wallin, 2000
CI Solvent Yellow 7	uptake	oral absorption	detected in fat		rats		Radomski, 1961 cited in Moller and Wallin, 2000

chemical	data type	descriptor	value	units	test matrix	method/parameters	reference
clofibrate	metabolism	human	90% excreted as conjugate or free drug				Estler, 1983; Mutschler, 1991; Zollner et al, 1992; Cited in Henschel et al, 1997
colchicine	metabolism	bile/plasma ratio	494			1 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
cyclophosphamide	metabolism	bile/plasma ratio	45.2			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
	metabolism	human	hydrolyses in water				Richardson and Bowron, 1985
	metabolism	human	50% excreted unaltered				Daughton and Temes, 1999
decamethonium	metabolism	bile/plasma ratio	<1			1 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
diatrozoate	metabolism	sewage treatment	metabolites not biodegradable				Kalsch, 1999; Cited in Daughton and Temes, 1999
diethylstilbesterol	metabolism	bile/plasma ratio	329			1 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
ellipticine	metabolism	bile/plasma ratio	538			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
enrofloxacin	metabolism	animals	unmetabolized 10	%			Vancutsum et al, 1990; Cited in Halling-Sorensen et al, 2000
fenofibrate	metabolism	human	rapid hydrolysis after ingestion				Daughton and Temes, 1999
fenofibric acid	metabolism		reactivated to parent in STP				Temes, 1998; Cited in Daughton and Temes, 1999
hycanthone	metabolism	bile/plasma ratio	14442.3			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
hydrochlorothiazide	metabolism	human	very little metab				Richardson and Bowron, 1985
	metabolism	human	very little metab				Richardson and Bowron, 1985
ifosamide	metabolism	human	20-50% excreted unchanged				Kummerer et al, 1997; Cited in Daughton and Temes, 1999
Ivermectin	ADME	metabolism/excretion - cattle	approx. 44.	%	% of parent drug unaltered in feces of steer		Halley et al. 1989
	ADME	metabolism/excretion - sheep	61	%	% of parent drug unaltered in feces of sheep		Halley et al. 1989
	ADME	metabolism/excretion - swine	39	%	% of parent drug unaltered in feces of swine		Halley et al. 1989
mefenamic acid	metabolism	human	some conjugation				Richardson and Bowron, 1985
methotrexate	metabolism	bile/plasma ratio	2203			1 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
	metabolism	human	no metabolism				Henschel et al, 1997
monensin	metabloism	animals	extensive		oral dosing		Donoho, 1984
neomycin	metabolism	human	1-6% absorbed				Richardson and Bowron, 1985
nicotinamide	metabolism	human	hydrolyses to nicotinic acid				Richardson and Bowron, 1985
nicotine	metabolism	bile/plasma ratio	65			1 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986

chemical	data type	descriptor	value	units	test matrix	method/parameters	reference
penicillin G	metabolism	bile/plasma ratio	20.8			20 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
pentobarbital	metabolism	bile/plasma ratio	6.8			10 ng/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
phenobarbital	metabolism	bile/plasma ratio	2.3			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
piperazine	metabolism	human	no metabolism				Richardson and Bowron, 1985
promethazine	metabolism	human	high 1st pass metab				Richardson and Bowron, 1985
propanolol	metabolism	human	4-OH-propanolol major metabolite				Daughton and Ternes, 1999
pseudoephedrine hydrochloride	metabolism	human	98% excreted unchanged				Richardson and Bowron, 1985
pseudoephedrine sulphate	metabolism	human	98% excreted unchanged				Richardson and Bowron, 1985
puromycin	metabolism	bile/plasma ratio	189			1 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
riboflavin-5-phosphate	metabolism	human	rapid metab				Richardson and Bowron, 1985
riboflavin-5'-phosphate sodium	metabolism	human	rapid metab				Richardson and Bowron, 1985
salbutamol	metabolism	human	high 1st pass metab				Richardson and Bowron, 1985
salicylic acid	metabolism	bile/plasma ratio	<1			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
sodium lauryl sulphate	metabolism	bile/plasma ratio	54.8			1 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
spironolactone	metabolism	human	metab to canrenone				Richardson and Bowron, 1985
sulfanilamide	metabolism	bile/plasma ratio	1.4			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
tetracycline	metabolism	bile/plasma ratio	73.6			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986
warfarin	metabolism	bile/plasma ratio	373.2			10 mg/kg intra vascular inj. Dogfish; 24h	Guarino and Lech. 1986

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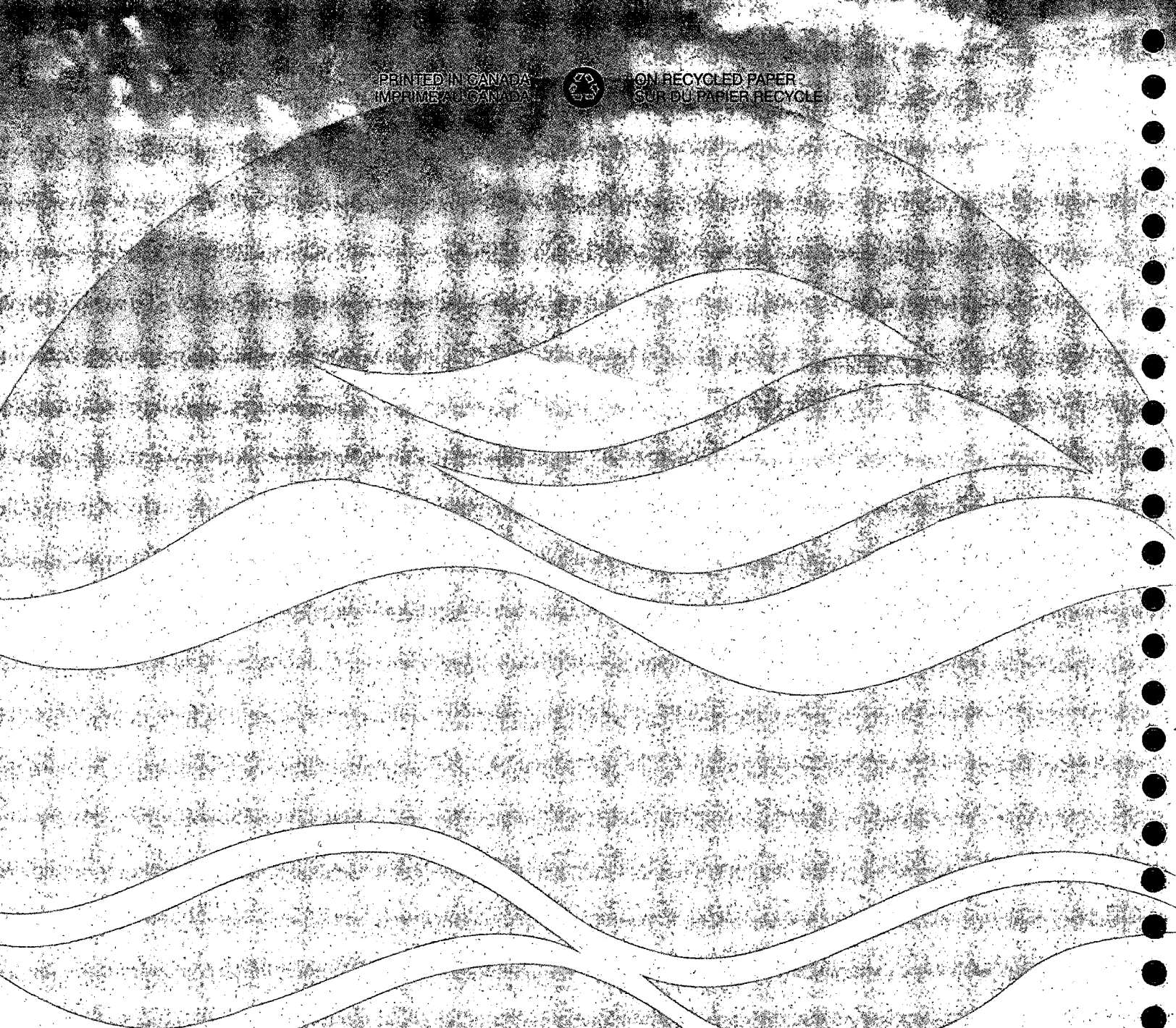

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