

PharmEcovigilance and the Environmental Footprint of Pharmaceuticals

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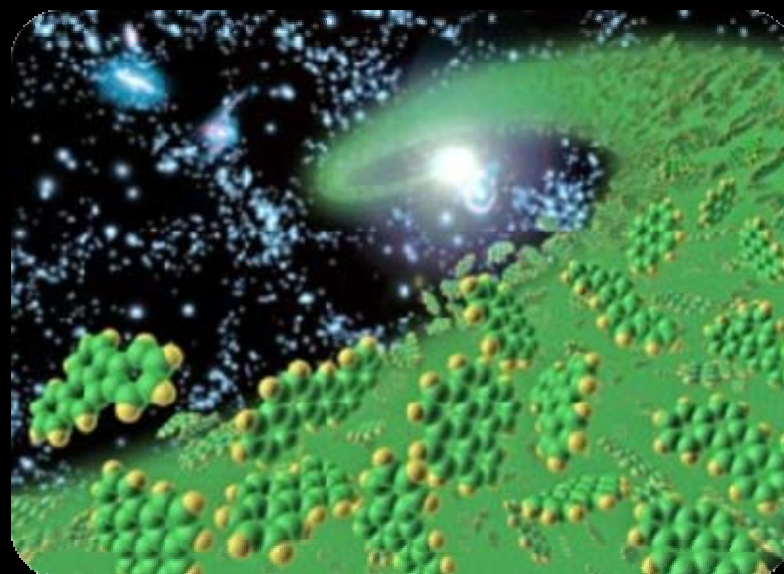
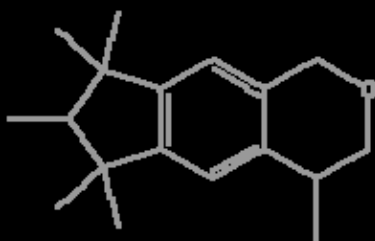
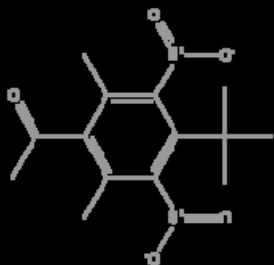
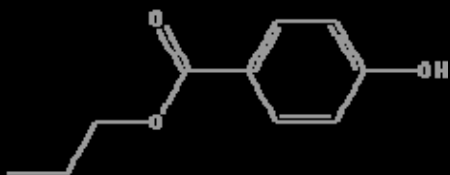


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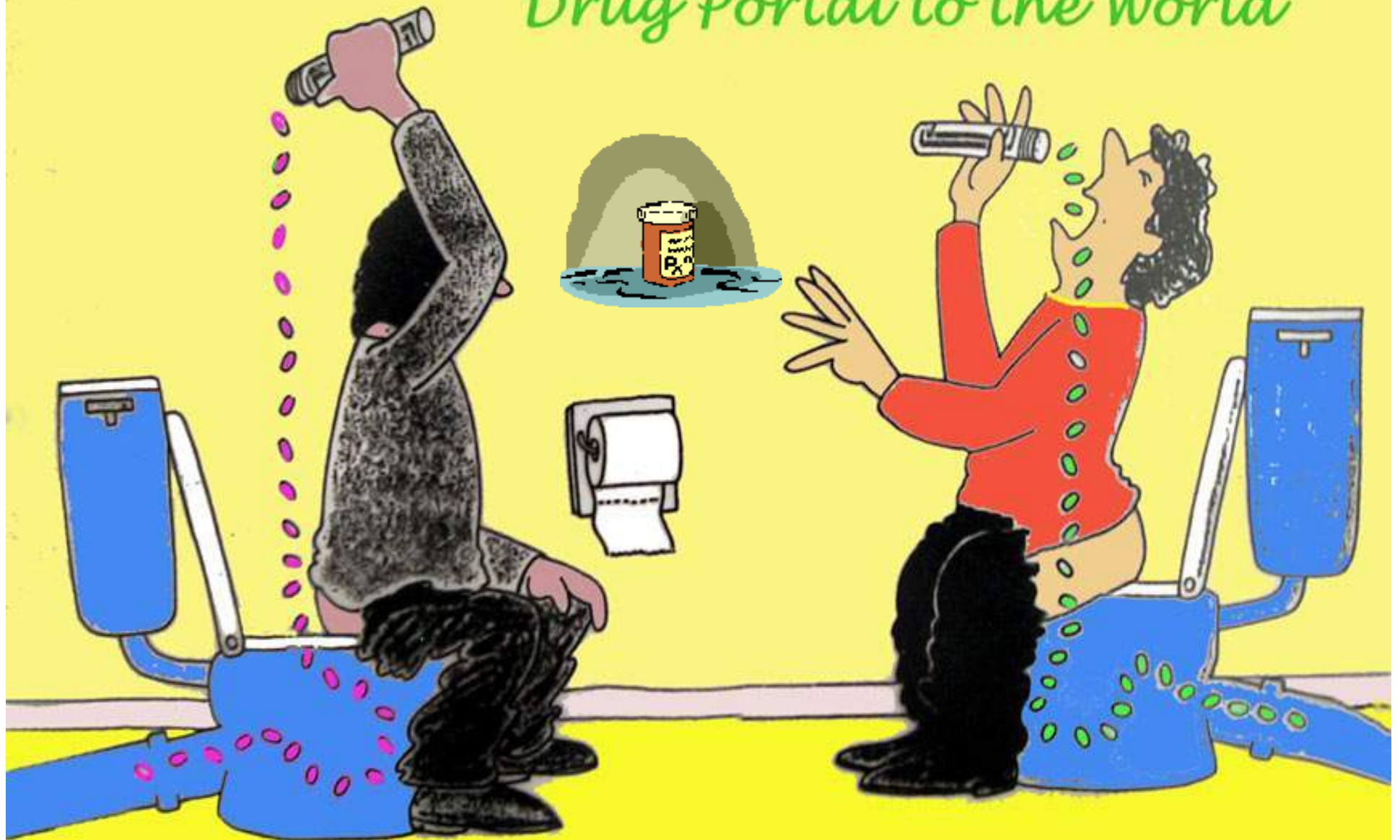
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PPCPs as Environmental Pollutants?

PPCPs are a diverse group of chemicals comprising all human and veterinary **drugs** (available by prescription or over-the-counter, including “biologics”), **diagnostic agents** (e.g., X-ray contrast media), “**nutraceuticals**” (bioactive food supplements such as huperzine A), and other consumer chemicals, such as **fragrances** (e.g., musks) and **sun-screen agents** (e.g., 4-methylbenzylidene camphor; octocrylene); also included are “**excipients**” (so-called “inert” ingredients used in PPCP manufacturing and formulation; e.g., parabens).



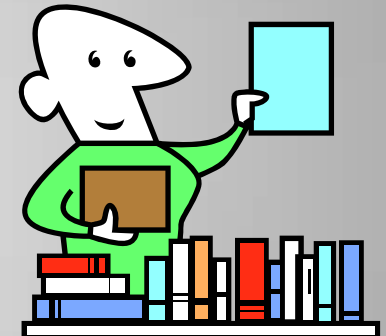
Drug Portal to the World



adapted by Daughton from Ternes (April 2000)

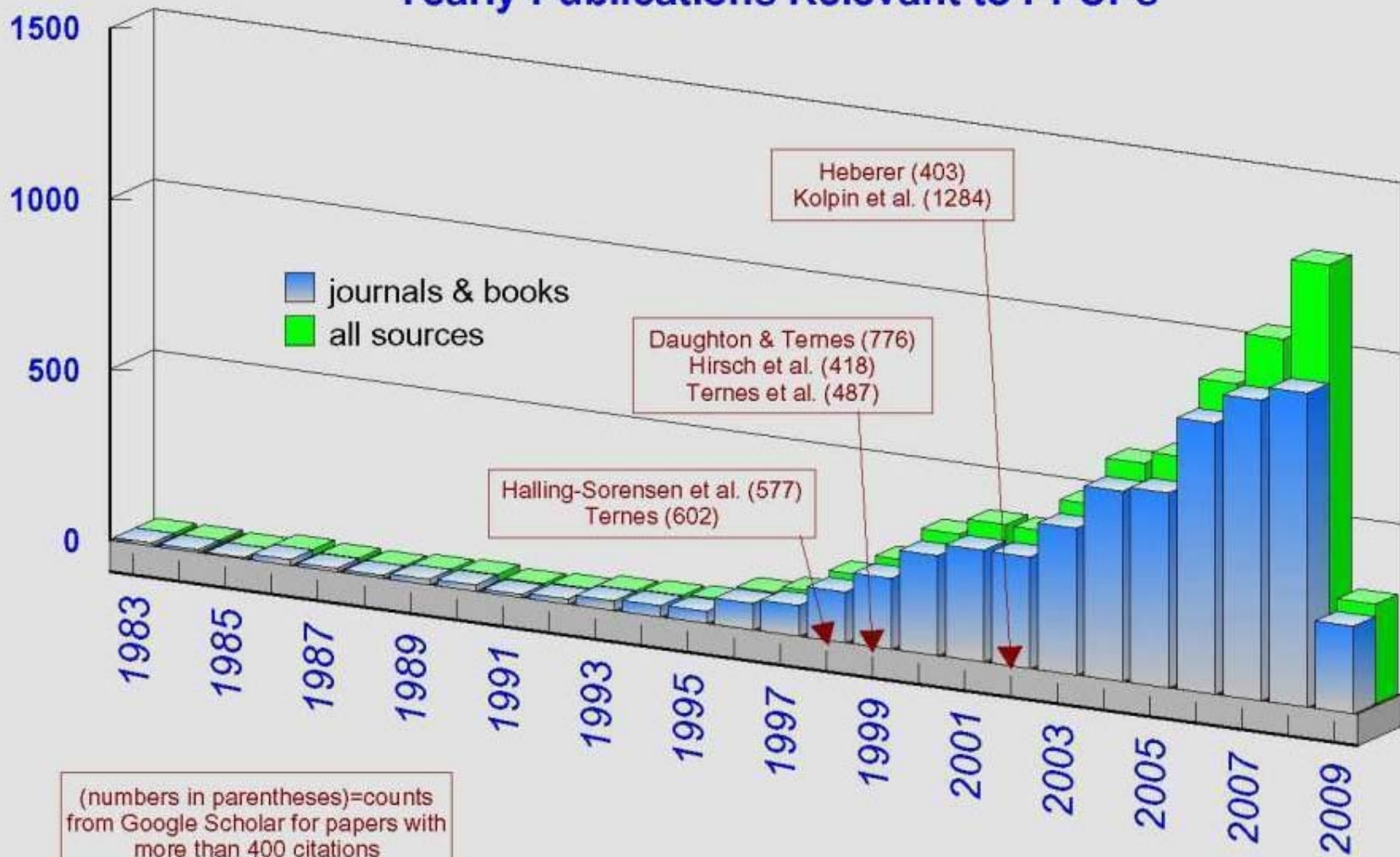
1st National Survey[†] Revealed Extent of PPCPs in Waterways

- **USGS “Reconnaissance” study in 1999-2000 was first nationwide investigation of pharmaceuticals, hormones, & other organic contaminants:**
 - 139 streams analyzed in 30 states
 - 82 contaminants identified (many were pharmaceuticals)
 - 80% streams had 1 or more contaminant
 - Average 7 contaminants identified per stream
- Since 1998, peer reviewed papers on PPCPs have increased from fewer than 200 per year to greater than 1,000 per year



[†] Kolpin DW, et al. "Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance." *Environmental Science & Technology* 2002, 36(6):1202-1211; doi:10.1021/es011055j

Yearly Publications Relevant to PPCPs



Source: DOI 10.1897/09-138.1

note: data for 2009 only through first 8 weeks

Prescription Drugs Found in Tap Water





Drug Disposal Overview



- Unused medications become pharmaceutical waste
 - Historically, consumers and other institutions have been advised to dispose of the drugs via the toilet or the trash
 - Ultimately can enter the environment
 - If not disposed, concern is availability for inappropriate usage of drugs
 - Diversion and poisonings
- Take-back events and programs
- Controlled Substances Act (CSA) 1970
- Stakeholders & Beneficiaries:
 - EPA, DEA, ONDCP, FDA, USFWS, state and local governments, municipal water districts, pharmacy & pharmaceutical industries, healthcare industry, insurance industry

PROBE FINDS PHARMACEUTICALS IN U.S. DRINKING WATER



Models of Change

- “Take-back” events
 - NERC
 - “No Drugs Down the Drain”
 - Great Lakes
 - US EPA grants
 - Various states
 - California, Pennsylvania, Indiana, Massachusetts, Oregon, Washington



National Guidance



- ONDCP original guidelines, February 2007
 - Collaboration with FDA and EPA
 - Updated October 2009; defers to FDA for list of drugs to be disposed via sewers
- DEA, Controlled Substances Act
 - Recent ANPRM
 - Encouraged to standardize process for what constitutes an exemption for law enforcement personnel
 - Encouraged to standardize recordkeeping requirements
 - Define what constitutes an appropriate destruction of controlled substances
 - Asked to consider many collection options for take back programs

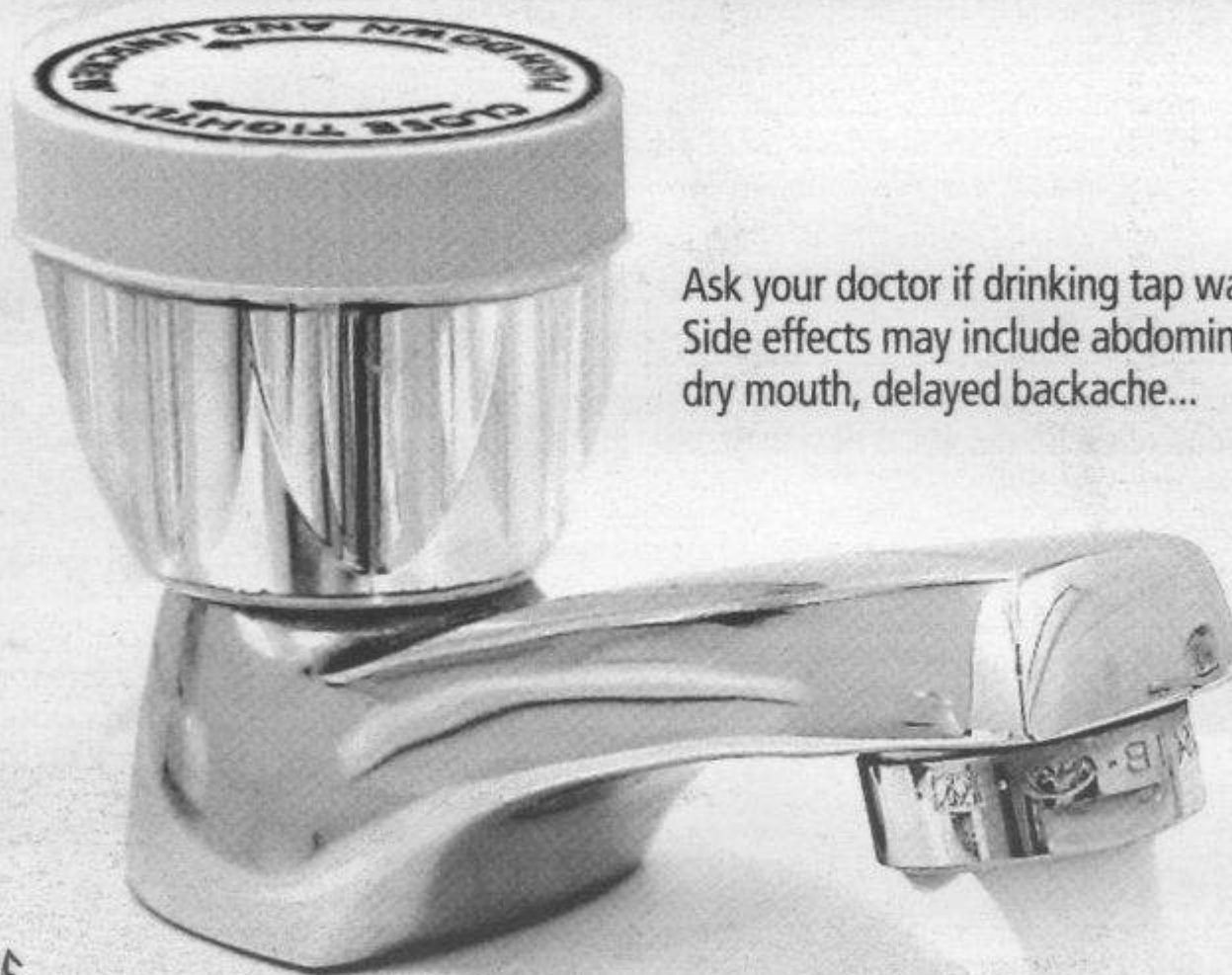
State Legislation

- **Maine, Minnesota, Oregon, and Florida** have legislation pending that would require drug manufacturers to operate and pay for statewide systems to collect, transport, and dispose of leftover pharmaceuticals from the public and certain facilities



Federal Legislation

- HR 1191 Safe Drug Disposal Act of 2009
 - Provide for disposal of controlled substances by ultimate users and care takers through state take-back disposal programs
 - Prohibits pharmaceutical company recommendations on drug labels for disposal by flushing
- HR 1262 The Water Quality Investment Act
 - Includes provisions requiring federal agencies to study the presence of pharmaceuticals and personal care products in the waters of the US



Ask your doctor if drinking tap water is right for you. Side effects may include abdominal pain, headache, dry mouth, delayed backache...

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A Clarification



- In this presentation, the actual chemical substances with which we are concerned regarding contamination of the environment are the active ingredients in pharmaceuticals – known in the industry as **APIs**. But we sometimes loosely (but incorrectly) refer to **drugs** or **pharmaceuticals** themselves as being the contaminants
- *These terms are all often used interchangeably*

ALIMENTARY TRACT AND METABOLISM STOMATOLOGICAL PREPARATIONS	Dolasetron Granisetron Ondansetron LAXATIVES Lactulose Doxycycline Clotrimazole Triamcinolone Epinephrine Amphotericin B Hydrocortisone Tetracycline Natamycin Chlorhexidine Metronidazole Aspirin Neomycin Minocycline Amlexanox Miconazole Dexamethasone	VITAMINS Paricalcitol Vitamin D4 (Dihydrothachysterol) MINERAL SUPPLEMENTS Calcium Acetate Magnesium Sulfate Potassium Chloride Calcium Chloride ANABOLIC AGENTS FOR SYSTEMIC USE Oxandrolone Nandrolone OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS Nitisinone Miglustat L-Carnitine Cysteamine	Calcium Chloride CARDIOVASCULAR SYSTEM CARDIAC THERAPY Phentermine Dofetilide Midodrine Milrinone Ranolazine Disopyramide Lidocaine Ibutilide Fumarate Mexiletine Phenylephrine Digoxin Acetyldigoxin Metaraminol Adenosine Epinephrine Methoxamine Nitroglycerin Alprostadil Fenoldopam Dobutamine Isosorbide Dinitrate Quinidine Levosimendan Dopamine Isosorbide Mononitrate Procainamide Ibuprofen Tocainide Deslanoside Arbutamine Amiodarone Bretiyilum Propafenone Flecainide Encainide	Amiloride Cyclothiazide Furosemide Eplerenone Hydroflumethiazide Indapamide Chlorothiazide Bumetanide Hydrochlorothiazide Trichlormethiazide PERIPHERAL VASODILATORS Phentolamine Nicergoline Tolazoline Pentoxifylline Phenoxybenzamine Ergoloid mesylate VASOPROTECTIVES Lidocaine Fluorometholone Betamethasone Sodium Tetracycl Sulfate Fluocinolone Acetonide Flumethasone Pivalate Pentosan Polysulfate Procaine Hydrocortisone Hydrocortamate Prednisolone Ethanol Fluocinonide Benzocaine Benzocaine Dexamethasone Ergonovine Fenofibrate Atorvastatin Fluvastatin Rosuvastatin Gemfibrozil	Felodipine Nifedipine Perhexiline Nifedipine Bepridil AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM Valsartan Ramipril Remikiren Olmesartan Medoxomil Fosinopril Trandolapril Benazepril Enalapril Losartan Moexipril Lisinopril Perindopril Candesartan Eprosartan Quinapril Telmisartan Irbesartan Captopril LIPID MODIFYING AGENTS Pravastatin Lovastatin Rosuvastatin Colestipol Clofibrate Simvastatin Colestevam Ezetimibe Fenofibrate Atorvastatin Fluvastatin Rosuvastatin Gemfibrozil	Flucytosine Miconazole Econazole Sertaconazole Ciclopirox PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS Isosorbide Dinitrate ANTIPRURITICS, INCL. ANTI-HISTAMINES, ANESTHETICS, ETC. Lidocaine Procaine Tripeleminamine Oxybuprocaine Proflavine Diphenhydramine Benzocaine Bromodiphenhydramine Trimeprazine ANTIPRURITICS Acetaminophen Methoxsalen Ibuprofen Erythromycin Adapalene Fluorometholone Chloramphenicol Azelaic Acid Prednisolone Methylprednisolone Isotretinoin Clindamycin Dexamethasone OTHER DERMATOLOGICAL PREPARATIONS Pimecrolimus Minoxidil Monobenzone Magnesium Sulfate Tacrolimus Finasteride	Fluocinolone Acetonide Triamcinolone Flumethasone Pivalate Hydrocortisone Mometasone Hydrocortamate Clotocortolone Prednisolone Methylprednisolone Clobetasol Fluocinonide Prednicarbate Budesonide Dexamethasone ANTISEPTICS AND DISINFECTANTS Hexachlorophene Chlorhexidine Ethanol Proflavine SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM Diethylstilbestrol Chlorotrianisene Conjugated Estrogens Etonogestrel Desogestrel Megestrol Levonorgestrel Dydrogesterone Progesterone Raloxifene Norgestrel Medroxyprogesterone Testosterone Estrone Estradiol Mifepristone Clomifene Dieneestrol Norgestimate Ethinyl Estradiol Fluoxymesterone UROLOGICALS Sildenafil Tropium chloride Morphine Sulfenacin succinate Alfuzosin Darifenacin Acetohydroxamic Acid Phentolamine Tamsulosin Terconazole Clotrimazole Chloramphenicol Oxytetracycline Furazolidone Butoconazole Nystatin Amphotericin B Natamycin Metronidazole	Tioconazole Ketoconazole Miconazole Econazole Candidin Ciclopirox Clindamycin OTHER GYNECOLOGICALS Cabergoline Carboprost Tromethamine Lisuride Naproxen Ritonavir Dinoprostone Leoprost Tromethamine Bromocriptine SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM Diethylstilbestrol Chlorotrianisene Conjugated Estrogens Etonogestrel Desogestrel Megestrol Levonorgestrel Dydrogesterone Progesterone Raloxifene Norgestrel Medroxyprogesterone Testosterone Estrone Estradiol Mifepristone Clomifene Dieneestrol Norgestimate Ethinyl Estradiol Fluoxymesterone UROLOGICALS Sildenafil Tropium chloride Morphine Sulfenacin succinate Alfuzosin Darifenacin Acetohydroxamic Acid Phentolamine Tamsulosin Terconazole Clotrimazole Chloramphenicol Oxytetracycline Furazolidone Butoconazole Nystatin Amphotericin B Natamycin Metronidazole	Terazosin Calcium Chloride Finasteride SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS PHENOLIC AND HYPOTHALAMIC HORMONES AND ANALOGUES Gonadorelin Nafarelin Carbetocin CORTICOSTEROIDS FOR SYSTEMIC USE Betamethasone Triamcinolone Prednisone Hydrocortisone Prednisolone Rimexolone Methylprednisolone Trilostane Dexamethasone THYROID THERAPY Liothyronine Fludrocortisone Levothyroxine Propylthiouracil CALCIUM HOMEOSTASIS Cinacalcet ANTIINFECTIVES FOR SYSTEMIC USE ANTIBACTERIALS FOR SYSTEMIC USE Erythromycin Azithromycin Moxifloxacin Cefotiam Doxycycline Lymecycline Sulfanilamide Cefmenoxime Cefmetazole Flucloxacillin Ertapenem Piperacillin Aztreonam Sulfadiazine Grepafloxacin Ampicillin Penicillin V Cefpiramide Ceftazidime Trimethoprim Chloramphenicol Loracarbef
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Clomocycline	Fluconazole	Pipobroman	Aminogluthethimide	Ibuprofen	Anileridine	ANTI-PARKINSON	Zaleplon	Bupropion	Lidocaine
Enoxacin	Anidulafungin	Cladribine	Progesterone	Dimethyl sulfoxide	Mepivacaine	DRUGS	Acetophenazine		Bacitracin
Amikacin	Caspofungin	Anagrelide	Flutamide		Levobupivacaine	Benzotropine	Melatonin	ANTIPARASITIC	Dyclonine
Dicloxacillin	Voriconazole	Carmustine	Toremifene	MUSCLE	Methoxyflurane	Cabergoline	Pimozide	PRODUCTS,	Chlorhexidine
Pefloxacin	Amphotericin B	Amscrine	Medroxyprogesterone	RELAXANTS	Benzocaine	Ropinrole	Methypyrrolon	INSECTICIDES AND	Cocaine
Cefotaxime	Ketconazole	Bleomycin	Nilutamide	Baclofen	Halothane	Morphine	Zopiclone	REPELLENTS	Neomycin
Vancomycin	Clorambucil	Chlorzoxazone	Chlorzoxazone		Tolcapone	Tolcapone	Estazolam	ANTIPROTOZOALS	Benzocaine
Cefdinir	Miconazole	Raltitrexed	Estradiol	Carisoprodol	Desflurane	Metixene	Quetiapine	Pyrimethamine	
Ciprofloxacin	Micafungin	Mitomycin	Fulvestrant	Metocurine Iodide	Ketamine	Trihexyphenidyl	Aripiprazole	Mefloquine	DRUGS FOR
Cephalexin	Itraconazole	Bexarotene	Exemestane	Methocarbamol	Sevoflurane	Procyclidine	Chlorprothixene	Quinine	OBSTRUCTIVE
Sulfamethizole		Vindesine	Letrozole	Gallamine Triethiodide		Pramipexole		Chloroquine	AIRWAY DISEASES
Carbenicillin	ANTIMYCOBACTERI	Gefitinib	Bicalutamide	Cisatracurium Besylate	ANALGESICS	Entacapone		Amodiaquine	Flunisolide
Oxytetracycline	ALS	Thioguanine	Anastrozole	Tizanidine	Tramadol	Atropine	S	Pentamidine	Theophylline
Linezolid	Aminosalicylic Acid	Vinorelbine		Rocuronium	Eletriptan	Apomorphine	Fluvoxamine	Tinidazole	Ipratropium
Demeclocycline	Dapsone	Valrubicin	IMMUNOSUPPRESSI	Atracurium	Biperiden	Biperiden	Amphetamine	Metronidazole	Beclothemasonone
Cefixime	Cycloserine	Streptozocin	VE AGENTS	Cyclobenzaprine	Morphine	Amantadine	Caffeine	Primaquine	Betamethasone
Tobramycin	Capreomycin sulfate	Gemcitabine	Methotrexate	Doxacurium chloride	Zolmitriptan	Selegiline	Citalopram	Atovaquone	Montelukast
Trovafoxacin	Ethambutol	Teniposide	Tacrolimus	Orphenadrine	Acetaminophen	Orphenadrine	Reboxetine	Proguanil	Zafirlukast
Nitrofurantoin	Pyrazinamide	Epirubicin	Sirolimus	Chlormezanone	Codeine	Pergolide	Venlafaxine	Trimetrexate	Fluticasone Propionate
Oxacillin	Ethionamide	Celecoxib	Azathioprine	Tubocurarine	Dihydroergotamine	Bromocriptine	Atomoxetine	Halofantrine	Piperazine
Procaine	Rifabutin	Altretamine	Mycophenolic acid	Dantrolene	Hydromorphone	Levodopa	Amitriptyline		Triamcinolone
Hetacillin	Clofazimine	Cisplatin	Thalidomide	Mivacurium	Methadone		Protriptyline		Dyphylline
Tetracycline	Isoniazid	Alitretinoin	Leflunomide		Oxycodone	PSYCHOLEPTICS	Mirtazapine	Anthelmintics	Epinephrine
Meropenem	Rifapentine	Oxaliplatin		ANTIGOUT	Clonidine	Lorazepam	Tacrine	Piperazine	Nedocromil
Roxithromycin		Erlotinib	MUSCULO-	PREPARATIONS	Lisuride	Ethchlorvynol	Methylphenidate	Ivermectin	Mometasone
Nalidixic Acid	ANTIVIRALS FOR	Cyclophosphamide	SKELETAL SYSTEM	Allopurinol	Butorphanol	Temazepam	Imipramine	Mebendazole	Terbutaline
Polymyxin B Sulfate	SYSTEMIC USE	Vincristine	ANTIINFLAMMATO	Probenecid	Propoxyphene	Ziprasidone	Fluoxetine	Diethylcarbamazine	Bitolterol Mesylate
Gentamicin	Vidarabine	Fluorouracil	RY AND	Sulfapyrazone	Pentazocine	Talbutal	Duloxetine	Levamisole	Salmeterol
Colistin	Oseltamivir	Pentostatin	ANTIRHEUMATIC		Sumatriptan	Pentobarbital	Nortriptyline	Praziquantel	Formoterol
Cinoxacin	Nelfinavir	Methotrexate	PRODUCTS	DRUGS FOR	Ergotamine	Olanzapine	Amoxapine	Oxamniquine	Amlexanox
Fosfomycin	Indinavir	Vinblastine	Nabumetone	TREATMENT OF	Fentanyl	Clobazam	Trazodone		Budesonide
Cefaclor	Nevirapine	Imatinib	Ketorolac	BONE DISEASES	Nalbuphine	Clozapine	Galantamine	ECTOPARASITICIDE	Aminophylline
Sulfapyridine	Idoxuridine	Clofarabine	Tenoicam	Zoledronate	Diffunisal	Meprobamate	Paroxetine	S, INCL.	
Tinidazole	Penciclovir	Pemetrexed	Celecoxib	Alendronate	Almotriptan	Sulpiride	Trimipramine	SCABICIDES,	COUGH AND COLD
Metronidazole	Tenofovir	Mitotane	Tolmetin	Ibandronate	Buprenorphine	Eszopiclone	Modafinil	INSECTICIDES AND	PREPARATIONS
Spectinomycin	Cidofovir	Daunorubicin	Rofecoxib	Clodronate	Aspirin	Alprazolam	Tranylcypromine	REPELLENTS	Morphine
Ceforanide	Famciclovir	Porfimer	Piroxicam	Risedronate	Naratriptan	Loxapine	Phenelzine	Lindane	Codeine
Mezlocillin	Entecavir	Irinotecan	Fenopropfen	Etidronate	Rizatriptan	Remoxipride	Minaprine	Benzyl Benzoate	Methadone
Dirithromycin	Rimantadine	Etoposide	Valdecocix	Tiludronate	Frovatriptan	Secobarbital	Donepezil	Malathion	Dextromethorphan
Netilmicin	Zidovudine	Dacarbazine	Diclofenac		Dezocine	Promazine	Maprotiline	Disulfiram	Benzonatate
Telithromycin	Ritonavir	Temozolomide	Sulindac	OTHER DRUGS FOR		Zolpidem	Rivastigmine		Guafenesin
Lomefloxacin	Foscarnet	Aminolevulinic acid	Flurbiprofen	DISORDERS OF THE	ANTIEPILEPTICS	Prochlorperazine	Memantine	RESPIRATORY	Hydrocodone
Neomycin	Zanamivir	Carboplatin	Etodolac	MUSCULO-	Pregabalin	Droperidol	Sertraline	SYSTEM NASAL	
Sulfamethoxazole	Efavirenz	Dactinomycin	Mefenamic acid	SKELETAL SYSTEM	Phenytoin	Methohexital	Doxepin	PREPARATIONS	ANTIHISTAMINES
Minocycline	Stavudine	Cytarabine	Naproxen	Quinine	Topiramate	Chlordiazepoxide	Nefazodone	Flunisolide	FOR SYSTEMIC USE
Gatifloxacin	Amprenavir	Methyl aminolevulinic acid	Phenylbutazone		Valproic Acid	Chlorpromazine	Desipramine	Ipratropium	Clemastine
Penicillin G	Delavirdine	Doxorubicin	Meloxicam	NERVOUS SYSTEM	Trimethadione	Buspirone	Moclobemide	Phenylephrine	Cetirizine
Norfloxacin	Lamivudine	Busulfan	Penicillamine	ANESTHETICS	Metharbital	Haloperidol	Escitalopram	Beclomethasone	Terfenadine
Amoxicillin	Adefovir Dipivoxil	Topotecan	Suprofen		Mephentoin	Trifluoromazine	Pemoline	Phenylpropanolamine	Buclizine
Azlocillin	Ribavirin	Mercaptopurine	Meclofenamate		Lamotrigine	Adinazolam	Clomipramine	Mupirocin	Doxylamine
Cefditore Pivoxil	Emtricitabine	Melphalan	Oxapropin		Carbamazepine	Hydroxyzine	Isocarboxazid	Betamethasone	Thiethylperazine
Streptomycin	Didanosine	Fludarabine	Auranofin			Thiopental		Framycetin	Dexbrompheniramine
Cefuroxime	Tipranavir	Capecitabine	Ketoprofen			Fluphenazine	OTHER NERVOUS	Fluticasone Propionate	Triprolidine
Levofloxacin	Zalcitabine	Procarbazine	Ibuprofen			Clorazepate	SYSTEM DRUGS	Triamcinolone	Cyproheptadine
Cefadroxil	Ganciclovir	Arsenic trioxide				Thioridazine	Nicotine	Epinephrine	Loratadine
Cloxacillin	Abacavir	Idarubicin	TOPICAL PRODUCTS			Midazolam	Methadone	Nedocromil	Azizole
Cefprozil	Atazanavir	Ifosfamide	FOR JOINT AND			Flurazepam	Carbachol	Mometasone	Azatadine
Gemifloxacin	Saquinavir	Estramustine	MUSCULAR PAIN			Risperidone	Pyridostigmine	Pseudoephedrine	Carbinoxamine
Oflaxacin		Mitoxantrone				Coprolamine	Cinnarizine	Prednisolone	Epinastine
Kanamycin	ANTINEOPLASTIC	Lomustine				Propiomazine	Acamprosate	Oxymetazoline	Tripeleminamine
Clindamycin	AND	Paclitaxel				Halazepam	Naltrexone	Azelastine	Brompheniramine
Sparfloxacin	IMMUNOMODULATI	Docetaxel				Clazepam	Riluzole	Levocabastine	Methdilazine
Clarithromycin	NG AGENTS					Clonazepam	Disulfiram	Budesonide	Ketotifen Fumarate
Ceftriaxone	ANTINEOPLASTIC	ENDOCRINE				Vigabatrin	Buprenorphine	Dexamethasone	Fexofenadine
	AGENTS	THERAPY				Phenacemide	Bethanechol		Desloratadine
ANTIMYCOTICS FOR	Masoprocol	Diethylstilbestrol				Levetiracetam	Pilocarpine	THROAT	Azelastine
SYSTEMIC USE	Bortezomib	Megestrol				Cocaine	Ambenonium	PREPARATIONS	Promethazine

Azelastine	Olopatadine	Polymyxin B Sulfate	Aminohippurate	Pivalate	Lapatinib	Pivmecillinam
Promethazine	Polymyxin B Sulfate	Gentamicin	Aminophenazone	Dexmedetomidine	Lenalidomide	Podofilox
Mequitazine	Gentamicin	Prednisolone	Amobarbital	Dibucaine	Leucovorin	Posaconazole
Diphenhydramine	Tropicamide	Chlorhexidine	Amyl Nitrite	Dicumarol	Levallorphan	Practolol
Chlorpheniramine	Acetazolamide	Neomycin	Anisindione	Dicyclomine	Levomethadyl Acetate	Pranlukast
Diphenylpyraline	Natamycin	Ofloxacin	Anisotropine	Digitoxin	Levorphanol	Probutol
Cyclizine	Prednisolone	Dexamethasone	Methylbromide	Dimenhydrinate	Lincomycin	Procterol
Bromodiphenhydramine	Dorzolamide		Ardeparin	Dimethylthiambutene	Lisdexamfetamine	Proprietarycizine
Trimeprazine	Loteprednol Etabonate	VARIOUS ALL	Arformoterol	Diphenidol	Lopinavir	Quinacrine
	Chlorhexidine	OTHER	Azacitidine	Divalproex sodium	Lubiprostone	Ramelteon
OTHER	Oxybuprocaine	THERAPEUTIC	Bacampicillin	Dromostanolone	Lumiracoxib	Rasagiline
RESPIRATORY	Rimexolone	PRODUCTS	Bambuterol	Drospirenone	Marimastat	Retapamulin
SYSTEM PRODUCTS	Bimatoprost	Hydroxocobalamin	Bentoquatam	Echothiophate Iodide	Mechlorethamine	Ridogrel
Nitric Oxide	Cocaine	Dexrazoxane	Benzphetamine	Edrophonium	Meclizine	Rifampin
Doxapram	Ketotifen Fumarate	Sevelamer	Benzquinamide	Enprofylline	Menthol	Rosoxacin
	Oxymetazoline	Pralidoxime	Benzthiazide	Ergonovine	Meperidine	Salbutamol
SENSORY ORGANS	Demecarium bromide	Deferoxamine	Benzylpenicilloyl	Erythrityl Tetranitrate	Mephentermine	Salicyclic acid
OPHTHALMOLOGIC	Netilmicin	Ethanol	Polylysine	Ethacrynic acid	Mesalazine	Salsalate
ALS	Apraclonidine	Edetic Acid	Bevantolol	Ethinamate	Metaxalone	Sitagliptin
Vidarabine	Azelastine	Physostigmine	Bezafibrate	Ethiodized oil	Methacycline	Sodium lauryl sulfate
Betaxolol	Lomefloxacin	Diazoxide	Bromfenac	Ethopropazine	Methimazole	Sorafenib
Erythromycin	Cyclopentolate	Amifostine	Bufotenine	Ethoxzolamide	Methotrimeprazine	Succinylcholine
Alclometasone	Physostigmine	Naloxone	Butabarbital	Ethynodiol Diacetate	Methylergonovine	Sulfametopyrazine
Idoxuridine	Nandrolone	Flumazenil	Butalbital	Etoricoxib	Methylphenobarbital	Sulfisoxazole
Medrysone	Neomycin	Fomepizole	Calcium Gluceptate	Fenoterol	Meticillin	Sulfosone
Lidocaine	Ganciclovir		Candoxatril	Floxuridine	Metyrosine	Sunitinib
Travoprost	Gatifloxacin	DIAGNOSTIC	Carbidopa	Flunitrazepam	Mibefradil	Telbivudine
Morphine	Penicillin G	AGENTS	Carphenazine	Flupenthixol	Mimosine	Temafloxacin
Dapiprazole	Norfloracin	Pentagastrin	Carprofen	Flurandrenolide	Mitiglinide	Testolactone
Fluorometholone	Streptomycin	Betazole	Cefalotin	Forasartan	Molindone	Tetrahydrobiopterin
Timolol	Emedastine	Ceruletide	Cefazolin	Fosphenytoin	Moricizine	Thiabendazole
Phenylephrine	Pilocarpine	Bentiromide	Cefepime	Gamma Hydroxybutyric Acid	Mycophenolate mofetil	Thiamylal
Carbachol	Levocabastine	Inulin	Cefotetan		Nafcillin	Thiopropazone
Ampicillin	Heparin	Gonadorelin	Cefpodoxime	Gentian Violet	Nelarabine	Thiothixene
Famciclovir	Levofloxacin	Magnesium Sulfate	Ceftibuten	Glibenclamide	Neostigmine	Tiaprofenic acid
Trifluridine	Dichlorphenamide	Histamine Phosphate	Cephaloglycin	Gliquidone	Nitazoxanide	Ticarcillin
Betamethasone	Ofloxacin	Metyrapone	Cephapirin	Glutethimide	Nitrazepam	Tigecycline
Chloramphenicol	Guanethidine	Tolbutamide	Cerulenin	Glycodiazine	Nitrofurazone	Trimethobenzamide
Dipivefrin	Kanamycin		Cevimeline	Glycopyrrolate	Norepinephrine	Troleandomycin
Framycetin	Brinzolamide	CONTRAST MEDIA	Chlormerodrin	Guanabenz	Norethindrone	Uracil mustard
Verteporfin	Levobunolol	Gadodiamide	Chloroxine	Guanadrel Sulfate	Novobiocin	Valaciclovir
Methylscopolamine	Metipranolol	Diatrizoate	Chlorthalidone	Halobetasol Propionate	Olsalazine	Valganciclovir
Ketorolac	Dexamethasone	Gadoversetamide	Cilastatin	Hesperetin	Omapatrilat	Varenicline
Amikacin		Gadoteridol	Cilostazol	Hexafluorenum	Orciprenaline	Yohimbine
Brimonidine	OTOLOGICALS	Gadobenate	Cinalukast	Bromide	Quabain	Zileuton
Carteolol	Lidocaine	Dimethylumine	Cinolazepam	Hexobarbital	Oxprenolol	Zuclopenthixol
Ciprofloxacin	Betamethasone	Gadopentetate	Clavulanate	Hexylcaine	Oxybenzone	
Piroxicam	Chloramphenicol	dimethylumine	Clenbuterol	Hydralazine	Oxymorphone	
Atropine	Hydrocortisone		Clidinium	Hydroxychloroquine	Paliperidone	
Clonidine	Tetracycline	DIAGNOSTIC	Colchicine	Hydroxypropyl cellulose	Palonosetron	
Sulfamethizole	Polymyxin B Sulfate	RADIOPHARMACEU	Colistimethate	Hydroxystilbamidine	Pamidronate	
Diclofenac	Gentamicin	TICALS	Conivaptan		Paramethasone	
Oxytetracycline	Prednisolone	Succimer	Cromoglicate	Isethionate	Pargyline	
Triamcinolone	Chlorhexidine		Crotamiton	Hydroxyurea	Paromomycin	
Sulfacetamide	Cocaine	UNCLASSIFIED	Cryptenamine	Icodextrin	Pemirolast	
Latanoprost	Neomycin	3-Methylthiofentanyl	Cyclacillin	Imipenem	Pentolinium	
Epinephrine	Miconazole	5-Methoxy-N,N-diisopropyltryptamine	Cycrimine	Indecanide	Perflutren	
Tobramycin	Dexamethasone		Danazol	Indomethacin	Phenazopyridine	
Fluorescein		Acenocoumarol	Darunavir	Iodixanol	Phenindamine	
Methazolamide	OPHTHALMOLOGIC	Acepromazine	Dasatinib	Iohexol	Pheniramine	
Flurbiprofen	AL AND	Aceprometazine	Decamethonium	Iopendylate	Phenmetrazine	
Nedocromil	OTOLOGICAL	Aciclovir	Decitabine	Iron Dextran	Phenobarbital	
Procaine	PREPARATIONS	Aliskiren	Deferasirox	Isoetharine	Phytonadione	
Hydrocortisone	Betamethasone	Almitrine	Delta1-	Isoflurophate	Picrotoxin	
Scopolamine	Chloramphenicol	Alseroxylon	dihydrotestosterone	Isopropamide	Pipotiazine	
Epinastine	Ciprofloxacin	Alverine	Desonide	Isoproterenol	Pirbuterol	
Tetracycline	Tetracycline	Amdinocillin	Desoxy corticosterone	Josamycin	Pivampicillin	

200 Top-Selling Prescribed Drugs (2006)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118	119	120
121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136	137	138	139	140
141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	159	160
161	162	163	164	165	166	167	168	169	170	171	172	173	174	175	176	177	178	179	180
181	182	183	184	185	186	187	188	189	190	191	192	193	194	195	196	197	198	199	200

Global Problem of Humanitarian Donations



Hospital collection site for donated pharmaceuticals (Banda Aceh, Indonesia)



Environmental Impact of Disposal

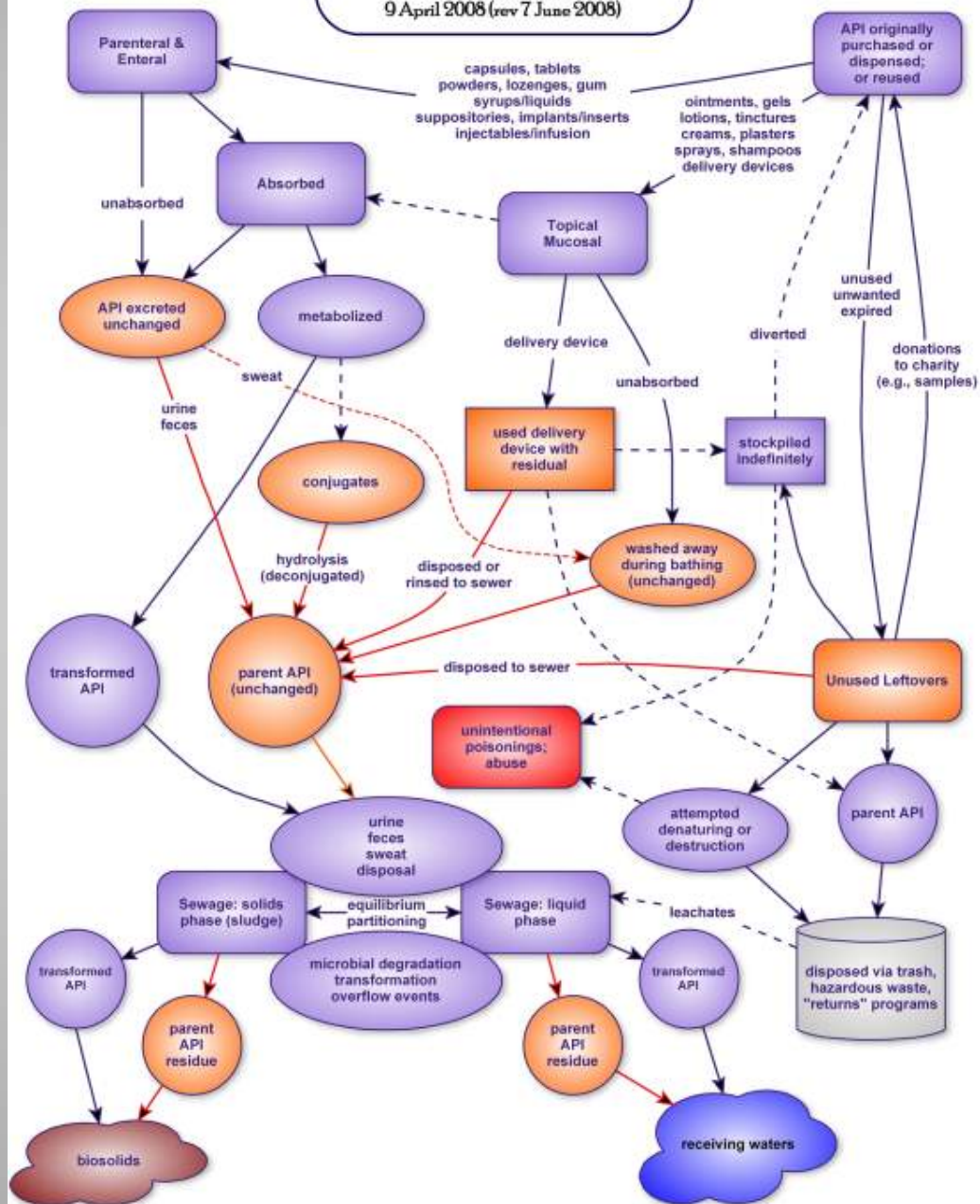
- APIs enter the environment by three primary routes: excretion, bathing, and disposal of leftover, unwanted medications
 - Excretion (primarily via urine and secondarily via feces) comprises continual low-level contributions from multitudes of people
 - Bathing releases APIs from medications applied directly to the skin and excreted via sweat ¹
 - Disposal represents acute but transient and episodic contributions from fewer people
 - The only route that is most amenable to pollution prevention or source control measures is disposal
- Indirect entry can occur via disposal of unwanted drugs and used delivery devices to trash (e.g., in leachates from landfills)
- **Proper disposal is greatly complicated by the conflict between the need to protect public safety (e.g., from drug diversion) and the need to minimize aquatic (and terrestrial) exposure**

¹ Daughton CG and Ruhoy IS "Environmental Footprint of Pharmaceuticals - The Significance of Factors Beyond Direct Excretion to Sewers," *Environmental Toxicology & Chemistry*, in press.



PharmEcokinetics of APIs

created by CG Daughton & IS Ruhoy
USEPA, Las Vegas
9 April 2008 (rev 7 June 2008)

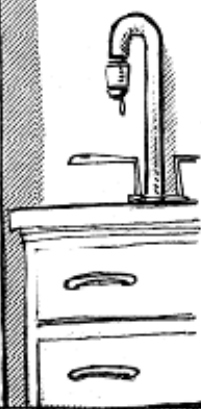
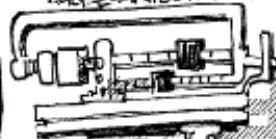




I'M GOING TO PRESCRIBE
A BIRTH CONTROL PILL AND AN
ANTIBIOTIC AND A TRANQUILIZER!
OR YOU CAN DRINK TWO QUARTS
OF TAP WATER, AND CALL ME IN
THE MORNING!



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COLUMBIA TRISTINE
DAILY TRISTINE
GAG-ECARTOONS.COM





Environmental Concerns

Treatment (palliative, symptomatic and sometimes curative) and prevention of disease, together with improved quality of life, are highly visible aspects of a global pharmaceutical industry with sales in 2007 exceeding US\$700BN

- Medicines are designed to have biological effects in small doses
 - Non-target organisms can be exposed
 - Possible subtle effects in aquatic organisms at very low concentrations (as low as ng/L or parts per trillion [ppt])
- There are thousands of chemically distinct APIs in medicines
 - Potential for additive or interactive effects with other medicines and/or other contaminants



Environmental Concerns

- Pharmaceutical Waste Streams
 - India; in one instance, the levels of the most abundant API [ciprofloxacin] reached 31 mg/L [31 ppm] at a waste treatment facility, orders of magnitude higher than had ever been reported (*Larsson et al. 2007*)
 - Unknown are the quantities of APIs flushed by health care facilities in the US



Environmental Pollution

- Water treatment
 - Situations where sewage receives minimal or no treatment
 - Septic systems, straight-piping, storm over-flow
 - Conventional
 - Coagulation, flocculation, depth filtration
 - Advanced
 - Chlorination
 - Ozonation, activated carbon, reverse osmosis, nanofiltration
- Some APIs are STILL refractory
 - For example, carbamazepine, ibuprofen, clofibric acid, 17 α -ethinylestradiol, meprobamate, dilantin, contrast agents, chemotherapeutics, some β -blockers
 - Not just parent APIs
 - Some metabolites, degradates, and transformation products can be more mobile, more persistent, and potentially as toxic

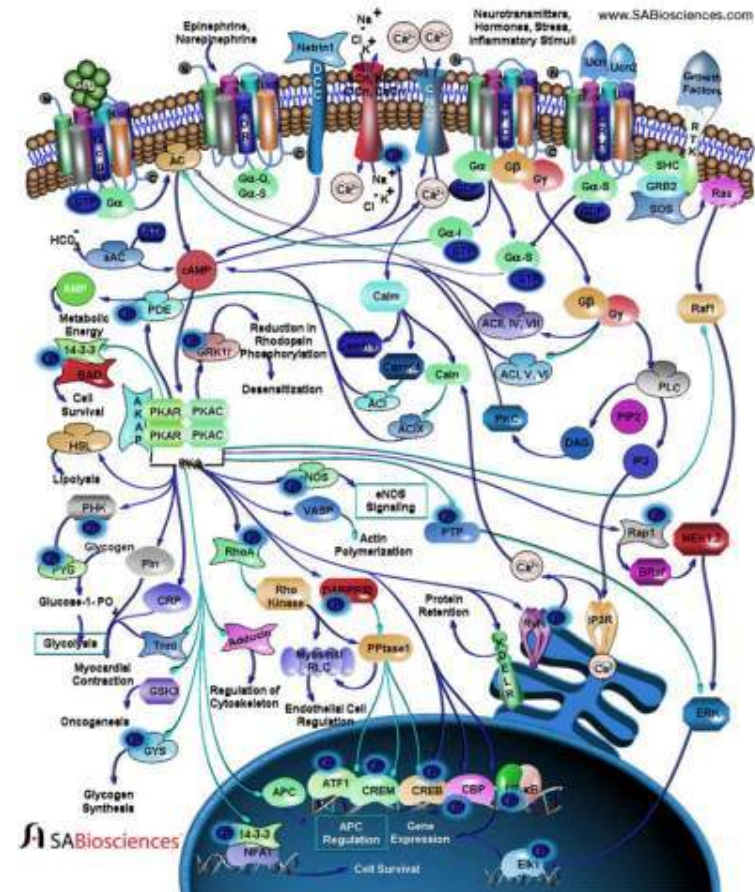
Effects on Aquatic Organisms: Cause for Concern

- “Pseudo-persistence” of APIs
 - Continuous, multigenerational exposure
- May be endocrine disruptors
 - alterations to sexual differentiation
 - Boulder Creek (feminization)
 - Potomac River (intersex)
 - reproduction and growth impairments
 - Antidepressants and frogs
 - subtle, behavioral effects
- More questions than answers about effects of APIs on aquatic species and the possibility of chronic effects in sensitive subpopulations of humans
- Little is known regarding bioconcentration



Effects

- Ecological
 - Sex ratios
 - Feminization
 - Behavioral/Social
 - Neurological
 - Growth
- Human Effects
 - Largely unknown
 - Food chain
 - Antibiotic resistance
- Unintended Exposure in Vulnerable Populations
 - Faeroe Island Statement
- FDA – environmental risk assessment

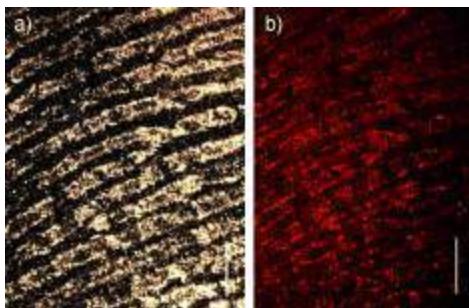


Human Exposure

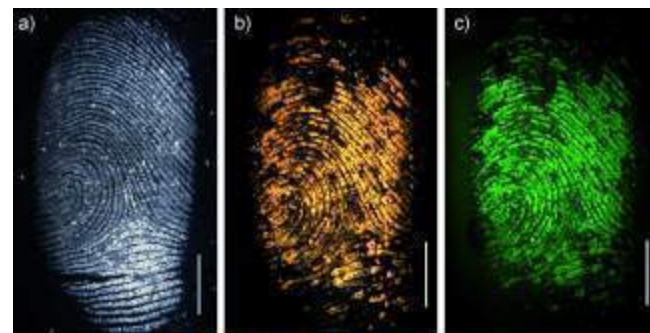
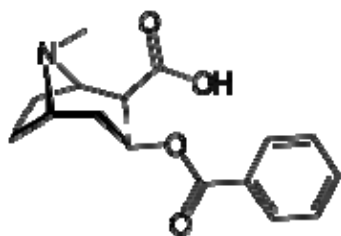
Function of:

- Identities, quantities, & geographic distribution of APIs
- ADME
- Environmental transport
- Environmental fate
- Exposure routes

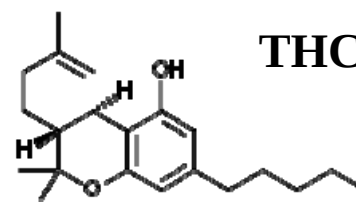
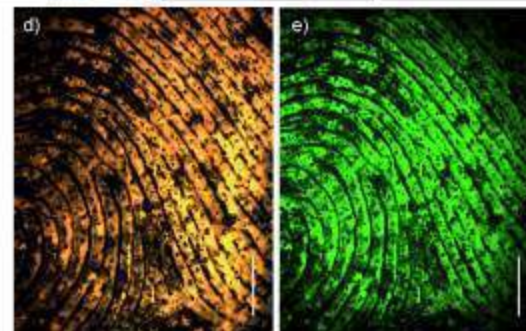
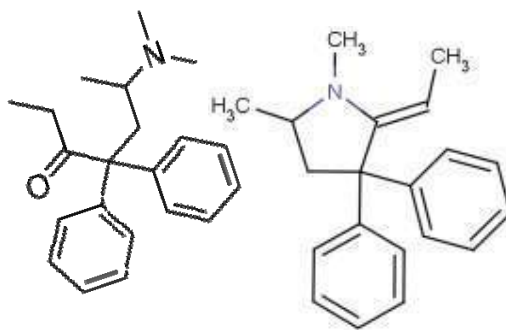
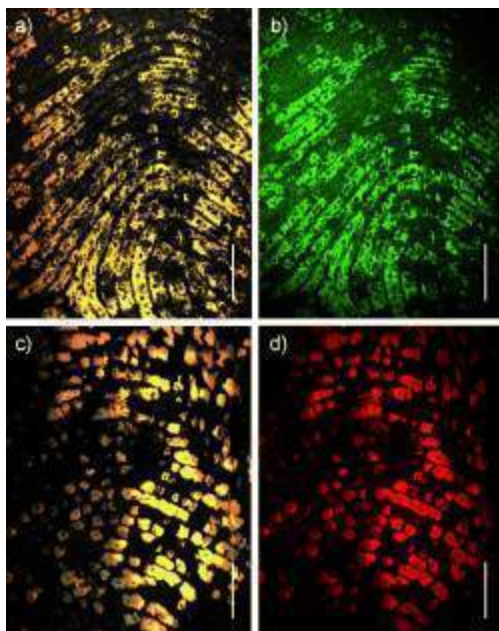
Fingerprints as contributors of environmental contaminants



benzoylecgonine



methadone & EDDP



THC

benzoylecgonine (major cocaine metabolite)

EDDP: 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (major methadone metabolite)

THC: Δ 9-tetrahydrocannabinol (main psychoactive of marijuana)

Hazarika P, Jickells SM, Wolff K, Russell DA (2008) Imaging of Latent Fingerprints through the Detection of Drugs and Metabolites. *Angew Chem Int Ed* 47:10167-10170.

Jack and Jill
went up the hill,
To fetch a pail
of water,
Jack fell down
and broke his crown,
And Jill gave him
painkillers in
the water...

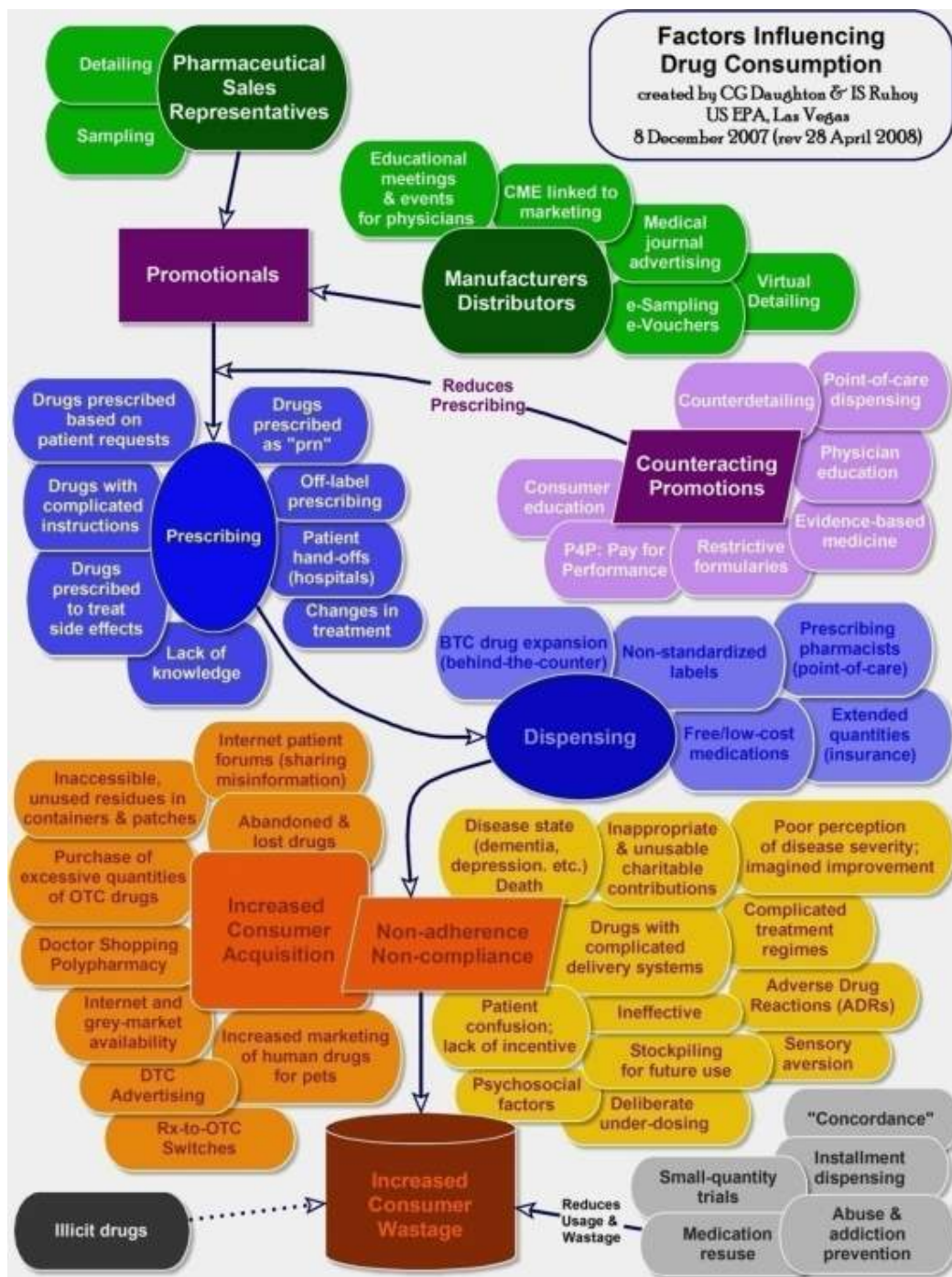


MARGULIES

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I'M NOT FEELING WELL. I'M GOING TO RUN OVER TO THE PHARMACY.





Ruhoy IS and Daughton CG "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environ. Internat.*, 2008, 34(8):1157-1169; doi:10.1016/j.envint.2008.05.002; available: <http://www.epa.gov/nerlesd1/bios/daughton/EnvInt2008.pdf>

Pharmaceutical Accumulation

- Consumer Homes
 - Both human and animal medicine
- Physician Offices and Clinics
 - Samples and in-office procedure use
- Veterinarian Offices
- Animal Shelters
- Dental Offices
- Hospitals
- Long-Term and Chronic Care Facilities
- Decedent Homes
- Donations
- Schools (confiscation and health care offices)
- Military Bases
- Shelters
- Dialysis Centers
- Transfusion Centers
- First Responder Services
- First-Aid Kits
- Border Check Points
- Customs (airline and freight)
- Confined Animal Feeding Operations (CAFOs)
- Agriculture
- Aquaculture
- Zoos
- Clan Labs
- Cemeteries
- Cruise Ships
- Prisons and Jails
- Humanitarian Organizations

Major Unknown

- **What fractions of drug residues occurring in the ambient environment result from discarding leftover drugs?**
 - No studies provided objective data from well-defined populations to support any type of conclusion
 - Data are needed on the types, quantities, and frequencies with which drugs accumulate as household waste

Mining Data for Types and Quantities of Disposed Drugs

- Understanding the categories and quantities of drugs disposed facilitates assessing potential impacts on both the environment and human health by helping:
 - health care practitioners to address inefficient prescribing and dispensing practices and patient non-compliance
 - environmental scientists to better target APIs for monitoring purposes
 - assessment of risk to human health from chronic and/or acute exposures
 - policymakers (including those in the insurance industry) to begin to understand and confront the growing issue of wasted and discarded medications.

*Summary of API Masses Disposed to Sewerage by a Coroner Office
during a 12-Month Period: Categorized by Therapeutic Class*

ATC Code	ATC Main Group	Quantity (mg) disposed	#of APIs	% of Total
A	Alimentary Tract	18,685,271	56	34.6
N	Nervous System	16,510,963	95	30.6
C	Cardiovascular System	6,331,976	71	11.7
J	Anti-infectives	5,608,735	45	10.4
M	Musculoskeletal System	3,851,949	21	7.1
R	Respiratory System	984,780	16	1.8
B	Blood	721,450	9	1.3
V	Various	622,800	1	1.2
P	Antiparasitics	236,269	2	0.44
L	Antineoplastics	186,013	14	0.34
G	GU System & Sex Hormones	146,440	23	0.27
H	Hormonal Preparations	50,601	10	0.09
S	Sensory Organs	4,375	1	0.008
D	Dermatologicals	3,420	3	0.006
TOTAL		53,945,042	367	

Ruhoy IS and Daughton CG "Beyond the Medicine Cabinet: An Analysis of Where and Why Medications Accumulate," *Environ. Internat.*, **2008**, 34(8):1157-1169; doi:10.1016/j.envint.2008.05.002; available:
<http://www.epa.gov/nerlesd1/bios/daughton/EnvInt2008.pdf>

Ultimate Objective: No Leftover Drugs

long-term focus should not be on how to properly dispose of drugs, but rather how to minimize the creation of drug waste



Key questions

- Released API occurrence in point-of-use drinking water and in foods
- Toxicological significance of long-term human exposure to multiple APIs at extremely low levels
- Vulnerable sub-populations
- Prioritization of individual drug entities with respect to human hazard
- Portion of residues that originates from disposal of unwanted medications versus excretion
- Portion of human poisonings resulting from accidental ingestion and abuse of diverted drugs that are stored
- Significance of antibiotic residues in environment with respect to evolution of pathogen resistance

Current Federal Activities

- Research—USEPA, USGS, FDA, CDC, NOAA, FWS, ARS, and others are evaluating environmental occurrence, effects, and treatment & stewardship options; coordination through Interagency PiE working group (under CENR).
- Policy
 - USEPA – UWR & Health Services Industry Study
 - DEA – CSA & impact on drug “take backs”
- Disposal guidelines
 - Office of National Drug Control Policy (revised 10/09)
 - US Fish & Wildlife/APhA/PhRMA SMARxT program



Mike Kaefer THE DENVER POST 05/13/08





Pharm*Ecovigilance*

- Conventional pharmacovigilance expanded beyond conventional focus on adverse drug reactions (ADRs) to encompass environmental concerns
- Unify the parallel but interconnected needs for protecting both human and ecological health

Actions to reduce APIs in the environment and protect human health & safety

- Unit dosing and trial scripts
- Low-quantity packaging of OTC medications
 - Increased monitoring of patient
- Reduce incentives for excessive purchasing
 - Personalized medicine (e.g., lower doses)
 - Reduce polypharmacy
- Environmental assessments of newly designed drugs
- Prescribers to factor in possible environmental impact
- Widespread implementation of sustainable take-back programs
- Improved record keeping of disposed pharmaceuticals by institutions



Models of Change

- European Union
 - “Green” drugs – requires pharmaceutical companies to analyze environmental risks of new drugs
 - Database available to physicians
- KNAPPE
 - **K**nowledge and **N**eed **A**ssessment on **P**harmaceutical **P**roducts in **E**nvironmental Waters
- In Sweden, systems for classification of drug environmental risk and hazard have been used for 5 years
- START: Management strategies for pharmaceutical residues in drinking water - Pharmaceuticals for Human Use: Options of Action for Reducing the Contamination of Water Bodies
- High Performance Pharmacy Framework

Stewardship

- Stewardship involves much more than prudent disposal of leftover drugs
 - Actions taken to reduce PPCPs in the environment will have collateral benefits in also capturing chemicals we are currently not aware of and may lessen human morbidity and mortality

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