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Inventory on the presence of pharmaceuticals in Dutch water

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Summary

Recent data from Germany and Switzerland indicate that pharmaceuticals are present in surface water, effluents of sewage treatment plants (STPs) and occasionally in drinking water.
The Dutch water supply companies deliver water of high quality. They have substantial and reliable information on the compounds present in the untreated water and in drinking water. No data were available, however, on the presence of pharmaceuticals in Dutch waters. Based on information on the situation in Germany and Switzerland it was judged relevant to obtain data on the Dutch situation.
A joint research project has therefore been established by Riwa, VEWIN and Kiwa to gain more insight in the Dutch situation.

Based on occurrence data from Germany and Switzerland and the logKow a selection has been made of 11 pharmaceuticals that were likely to be present in Dutch waters as well. Analytical methods have been developed and implemented. Surface water, STP effluent and drinking water were analysed at several locations in the Netherlands and at one location in Belgium. The maximum concentrations ranged from 0.31 µg/l (carbamazepine) in surface water to 0.90 µg/l (eryhthromycine) in STP effluent. In drinking water no pharmaceuticals were detected in concentrations above the detection limit. The recovery of the applied, provisional, analytical methods is still low for some of the pharmaceuticals. The real concentrations might be a factor 2-10 higher and as a consequence the performance characteristics of these analytical methods need to be improved.

No pharmaceuticals were detected in drinking water in concentrations above the detection limit and an effect on human health seems very unlikely. Even if water is consumed with the concentrations that were observed in surface water, effects would be unlikely as the margin between the doses used in therapy and the concentrations in water is large.

In view of the new Drinking water Directive (98/83/EC) it has become more important to inform the consumer on the quality of its drinking water. To inform them well and keep their confidence it will be necessary to have reliable and representative data on the Dutch situation.
In this report only a first overview on the Dutch situation is given. To obtain a profound view on the Dutch situation more data are needed on the occurrence of pharmaceuticals in (small and large) surface waters, STPs and drinking water.

1 Introduction

Many anthropogenic compounds have been detected in the aquatic environment. These include industrial chemicals, agrochemicals (pesticides), detergents, plasticizers and others. Previous studies have also shown that some pharmaceutical compounds can as well reach detectable concentrations in the environment (Richardson & Bowron, 1985; Stan *et al.*, 1994, Ternes, 1998).
Hormones and antibiotic agents have already been detected in sewage-effluents, sediments and soils some twenty years ago (Waggott, 1981). More recently many other pharmaceuticals have been detected in sewage effluents and surface water (and occasionally in ground- and drinking water) as a result of the application of more sophisticated analytical techniques. Often these techniques were applied in the search for very low levels of pesticides and their metabolites.
Most data on the occurrence of pharmaceuticals are reported from Germany, Switzerland and Great Britain. In other countries pharmaceuticals will most probably be present in water but analyses are absent, scarce or not available in open literature.

A joint research project has been established by Riwa, VEWIN and Kiwa to obtain more information on the situation in the Netherlands. As most data from Germany and Switzerland are on human pharmaceuticals and also to delineate the project, only human pharmaceuticals were taken into consideration in the current survey.

In this report a first overview is presented on the present state of knowledge about the concentrations of human pharmaceuticals detected in European countries and the concentrations in the Netherlands and at one location in Belgium. In addition, information is given about the therapeutic dose and the concentrations observed in the different types of water. Finally the consequences for the drinking water supply are discussed.

2 Regulation of pharmaceuticals

Before a pharmaceutical can be placed on the market in the Netherlands it has to obtain a registration from the Medicines Evaluation Board (MEB). In order to obtain a registration a dossier has to be submitted to the MEB about the quality, safety and activity of the pharmaceutical.

The registration dossier has to fulfil European requirements and consists of 4 parts:
Part 1: administrative information and a summary
Part 2: chemical-pharmaceutical information (information on composition, preparation and quality control)
Part 3: pharmacological-toxicological information (information obtained in experimental animals on toxicology and mode of action)
Part 4: clinical-pharmacological information (information on the mode of action and safety of the pharmaceutical in humans)

Before a pharmaceutical is administered to humans a "safe toxicological research program" has to be conducted. Recently this program has been harmonised in the major industrial countries within the framework of the International Conference on Harmonisation. The concerning Note for Guidance gives a rough description of the studies necessary.
Evaluation by the Regulatory Authorities in the Netherlands only takes place in the registration phase, that means, if the producer is of the opinion that there are sufficient data to substantiate the mode of action and safety of the pharmaceutical. After the reports of the producer have been judged by the experts a final decision is made by the Medicines Evaluation Board. If the pharmaceutical is judged positively the product is entered in the Registry of Pharmaceuticals.

The most important aspects of the evaluation of a pharmaceutical are then the mode of action, safety and the quality of the pharmaceutical. Environmental aspects like expected concentrations in the environment or ecotoxicological effects caused by use of the pharmaceutical are not taken into account. In 1994 a draft guideline has been developed by the European Commision with a procedure for evaluating possible risks of the use of human pharmaceuticals for the environment. This draft guideline has been withdrawn in 1995 and no further guidelines on this subject have been developed since. An exception are pharmaceuticals based on genetically modified organisms (GMO's). In their evaluation environmental aspects are taken into consideration as well. However the evaluation is still according to a draft guideline and there are no guidelines on how to decide if there would be risk for the environment.

For the registration and evaluation of veterinary pharmaceuticals in 1995 an EU-guideline has been developed, which states that environmental aspects should be taken into account. This guideline is implemented in two phases. From 1998-2003 only concentrations in the environment have to be calculated. If the concentration is above the threshold level, studies on the effects of these concentrations have to be conducted. This will be obligatory from 2003.

If pharmaceuticals are found in the environment these aspects could be taken into consideration during the registration procedure, comparable to the registration procedure of pesticides. However, at the evaluation of pharmaceuticals a risk-benefit analysis is made for the wanted and unwanted effects in humans. If there is no other cure for that specific disease, the unwanted effects are taken for granted. How unwanted environmental effects should be fit into this approach will be a complex problem.

3 Pharmaceuticals in the environment

3.1 Emission and distribution

There are several routes by which human and veterinary pharmaceuticals can enter the environment. The three most important routes are:

- direct disposal at manufacturing;
- excretion with urine and faeces (sewage water);
- dispersion of manure on farming land and runoff.

The amount of pharmaceuticals that can be discharged by the producer to the sewage can be 1-5% of the total production. This is low, compared to other types of industry. Industrial waste water may be a possible source for the contamination of surface waters, but is probably not responsible for the ubiquitous occurrence of pharmaceuticals (Richardson & Bowron, 1985).
Holm *et al.* (1995) analysed the ground water downgradient of a landfill formerly used for the disposal of waste from pharmaceutical production. They found a large variety of sulphonamide concentrations ranging up to 5 mg/l. This pathway, however, only represents a point discharge effecting a limited area.
Stan *et al.* (1994) and Ternes (1998) concluded that the concentrations of pharmaceuticals and their metabolites observed in water samples were not from point sources, but originated from therapeutic use, as indicated by their widespread distribution in municipal sewage treatment plants (STPs).

The fate of veterinary and human drugs after urinal or faecal excretion differ considerably from each other. In general municipal sewage and, therefore, human pharmaceuticals have to pass through a STP prior to entering rivers or streams. Veterinary drugs are more likely to contaminate soil and ground water (without previous waste water treatment) when liquid manure is used for top soil dressing and will therefore probably be less important for surface water. After rainfall incidents surface waters can be polluted with both human or veterinary drugs by run-off from fields or agricultural areas treated with digested sludge or livestock slurries respectively. The influence of run-off on the distribution of veterinary pharmaceuticals to both surface water and groundwater should not be discarded in the long run.

Also drugs disposed with domestic waste can reach landfill sites which could lead to ground water contamination by leaching (Holm *et al.*, 1995). A unique pathway for the contamination of soil and ground water by residues of pharmaceuticals, derived from human application, may be the disposal of raw sewage or STP effluents by spray and broad irrigation in agricultural areas.

The fate of pharmaceuticals in the environment is presented in figure 1.

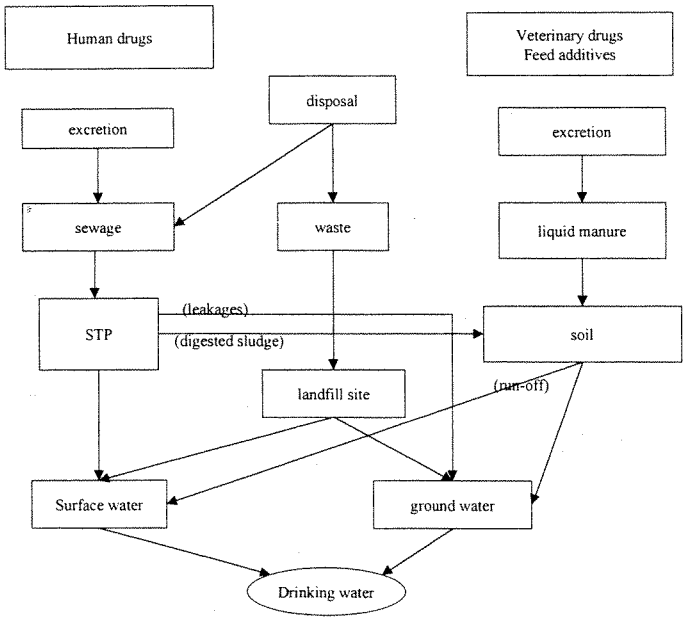


Figure 1. The fate of pharmaceuticals in the environment

3.2 Occurrence of pharmaceuticals in water

The last three years monitoring of pharmaceuticals has been a subject of intense research, especially in Germany and Switzerland. The general results of these surveys are discussed below.

3.2.1 Sewage effluent

Recent studies concerning pharmaceutical residues in the aquatic environment have clearly shown that the concentrations of pharmaceuticals in the influent of STPs can be up to the µg/l concentration range. Concentrations detected in substreams in the influent of a STP in Germany are presented in table 1.

Next to this it was established that elimination in municipal treatment plants is often incomplete. Ternes (1998) determined elimination rates ranging from 7% (carbamazepine) to 99% (salicylic acid) for a variety of medium polar drugs during sewage treatment. Generally more than 60% of the drug residues detected in the influent were removed. Only carbamazepine, clofibric acid, phenazon and dimethylaminophenazon showed lower average removal rates. Fenofibrate, acetaminophen and the metabolites of acetylsalicylic acid (salicylic acid, *o*-hydroxyhippuric acid, gentisic acid) were not detectable in the discharge to the river, although sometimes relatively high concentrations (up to 54 µg/l for salicylic acid) were determined in the influent. Hence, these drugs and metabolites were efficiently removed by the selected municipal STP (Ternes, 1998). Data on the elimination of several pharmaceutical are presented in table 2.

Table 1. Concentrations of pharmaceutical detected in (substreams of) influents of sewage treatment plants (from Stumpf et al., 1996; Buser et al., 1999, Stumpf et al., 1999)

Compound or breakdown product	oncentration in ng/l
bezafibrate	3000 1200
clofibric acid	14000 1000
diclofenac	2000 750
fenofibric acid	2000 450
gemfibrozil	4000 300
ibuprofen	12000 990-3300 300
indometacine	950
ketoprofen	550
naproxen	600

Table 2. Elimination of different pharmaceuticals during passage through a municipal sewage treatment plant (from Ternes, 1998 Ternes et al., 1998 and Buser et al., 1999)

Compound	Elimination percentage
acetylsalicylic acid	81%
bezafibrate	83%
biphenylol	98%
carbamazepine	7%
chlorophene	63%
clofibric acid	51%
diclofenac	69%
dimethylaminophenazone	38%
fenofibric acid	64%
gemfibrozil	69%
ibuprofen	90-99%
indometacine	75%
metoprolol	83%
naproxen	66%
phenazon	33%
propanolol	96%

Many antibiotics are polar (see annex III) and may not be eliminated effectively, as elimination is for the larger part achieved by adsorption on activated sludge which is partly mediated through hydrophobic interactions. In addition, many other authors have found pharmaceuticals or metabolites in sewage effluent. Concentrations detected in sewage effluent range from < 0.05 µg/l up to 4.6 µg/l and 6.3 µg/l for bezafibrate and carbamazepine, respectively (Ternes, 1998) (see annex 2).

3.2.2 *Surface water*

In annex 1 the available occurrence data on pharmaceuticals in surface water are summarised. In rivers and streams pharmaceuticals can be present in concentrations up to 3 µg/l but the concentrations are usually in the ng/l range. Some compounds can be detected continuously, others only with intervals or only in certain streams or parts of the river.

3.2.3 *Groundwater*

There are some references concerning findings of metabolites of pharmaceuticals in groundwater, but most of them are associated with landfills (Holm *et al*, 1995).
Hirsch *et al.* (1999) analysed ground water samples taken in areas with extensive livestock breeding for antibiotics but found no detectable concentrations.
Van Gool (1993) has estimated that if the total amount of growth promoters as used in the Netherlands was spread over the 2 million hectares of arable land, a yearly average of 130 mg antibiotic and metabolites per m^2 arable land would be found. These figures may be alarming, but the soil will act as an enormous buffer to enable (bio)degradation of these products, before leaching to the groundwater will occur. Groundwater will be less exposed by (metabolites of) human pharmaceuticals than by veterinary pharmaceuticals. In this study only human pharmaceuticals were taken into consideration but to obtain an overview on the quality of ground water veterinary pharmaceuticals should be taken into account as well.

Although leaching to groundwater of more polar human pharmaceuticals cannot be excluded (neither an effect on the terrestrial ecosystem), research is at first focussed on the presence of pharmaceuticals in surface water. The risk of contamination of drinking water prepared from surface water seems more realistic.

3.2.4 *Drinking water*

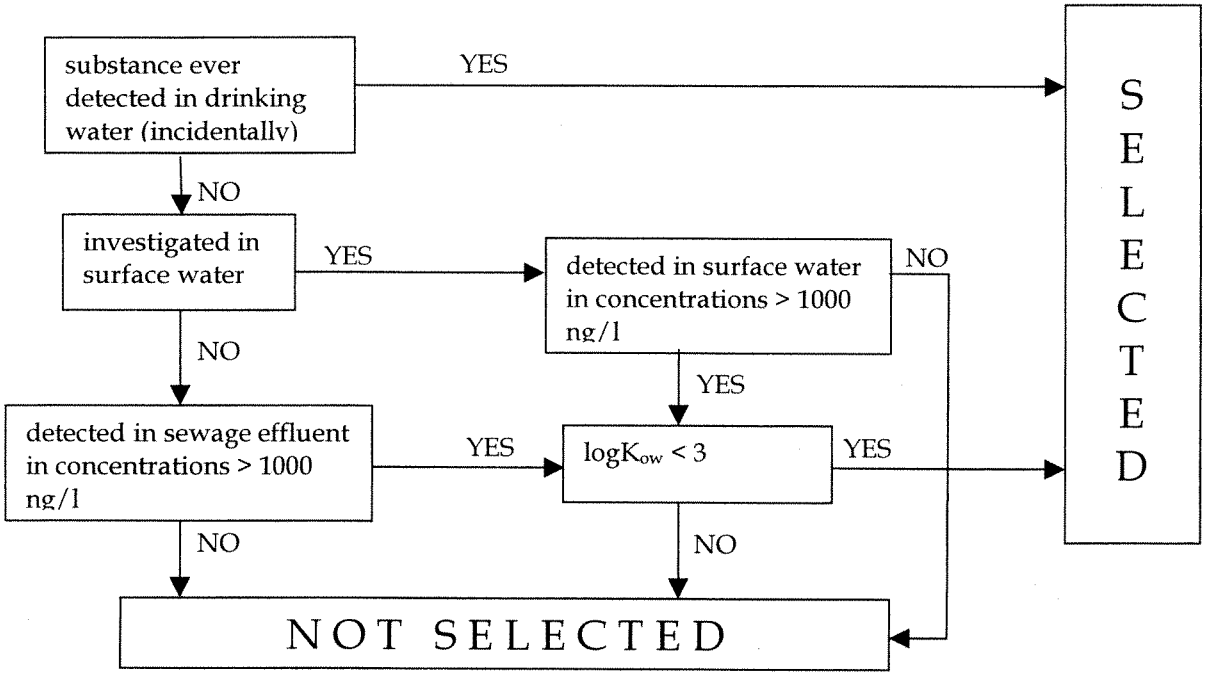
Not much is known about the presence of pharmaceuticals in drinking water but occasionally pharmaceuticals are detected in drinking water (annex 1). Apart from clofibric acid and diclofenac their presence was only confirmed in less that 5% of the drinking waters sampled.
Concentrations observed in drinking water are mostly in the ng/l range.
The removal of pharmaceuticals during drinking water treatment depends on the pharmaceutical. Sacher *et al.* (1998) found that carbamazepine is not totally removed during soil passage as it was also detected in bank filtrated water used for drinking water production. Stan *et al.* (1994) concluded that clofibric acid was not totally eliminated during drinking water treatment when bank filtrate or surface water was used.
On the other hand Hirsch *et al.* (1996) investigated some betablockers and β-sympathomimetics and these were completely eliminated by activated carbon filtration.

4 Concentrations observed in the Netherlands

As one of the objectives of this study was to obtain a general overview on the situation in the Netherlands, analyses have been performed on a selected number of pharmaceuticals. Given the large number of pharmaceuticals in use, it is impracticable to monitor water samples for all active ingredients involved. Therefore a selection has been made, based on occurrence in surface water (annex 1) and sewage treatment plants (table 1 and annex 2), and expected removal at drinking water treatment (indicated by the log K_{ow}, see annex 3).
As a rough estimate it can be stated that compounds with a log $K_{ow} < 3$ are able to pass the treatment system (when infiltration or activated carbon is applied).

The selection procedure is presented below. After each selection step an expert judgement is still necessary to judge the relevance of the selected pharmaceutical.

Figure 2. Selection scheme



If no data on detection are available, a pharmaceutical can still be important based on data of the prescribed amounts. An analytical method should then be developed or adapted as well. Data on the use of pharmaceuticals in the Netherlands are not yet available but will be reported by RIWA in 2000.

In view of the criteria mentioned above, pharmaceuticals selected were:

Acetyl salicylic acid
Bezafibrate
Bisoprolol
Carbamazepine
Clofibric acid
Diclofenac
Erythromycine
Fenofibrate
Hydroxy ibuprofen (metabolite of ibuprofen)
Ifosfamide
Metoprolol
Paracetamol
Sulphamethoxazol
Tetracycline

For each of these compounds a LC/MS/MS analytical method was developed. The LC/MS/MS analysis was conducted with Electrospray as an interface, both in the positive and negative ionisation mode.

The concentrations are presented in table 3. It should be stressed that the analytical method was developed to provide indicative concentration levels. Further optimisation of the method should be carried out to improve the reliability of the results up to the level for quantitative analysis. For some of the compounds like paracetamol, sulfamethoxazol and ifosfamide the recovery is still very low (between 0% and 20%). This means that the actual concentrations could be much higher (up to 2-10 times the presented concentration). However, for some pharmaceuticals e.g. bezafibrate, ibuprofen, diclofenac and fenofibrate, the recovery was already quite well (> 75%).

No results could be obtained for acetyl salicylic acid, bisoprolol and tetracycline as the LC/MS/MS, multi-method was not fit to include salicylic acid and tetracycline. Bisoprolol was not available as a pure component, which made the development of tha analytical method impossible.

Table 3. Concentrations of 11 pharmaceuticals investigated in different types of water in the Netherlands and at one location in Belgium (in µg/l) .

Sample	Paracetamol	Sulfametoxazol	Metoprolol	Ifosfamid	Erythromycin	Clofibric acid	Bezafibrate	Carbamazepine	Ibuprofen	Diclofenac	Fenofibrate
Surface water											
A	- -*	- -*	0,02	-	0,03	0,02	< 0,02*	0,19	0,01	<	-
C	- -*	0,02 0,02*	-	-	0,01	<	- -*	0,05	<	-	-
E	- -*	- -*	<	-	0,01	0,01	- -*	0,09	<	-	-
G	- -*	0,01 - *	0,03	-	0,03	0,02	< 0,02*	0,11	0,04	<	-
H	- -*	- <*	0,03	-	-	0,02	< 0,02*	0,12	0,03	-	-
J	- -*	- 0,01*	<	-	-	<	- -*	0,05	-	-	-
M	- -*	0,06 0,07*	-	-	-	0,02	0,02 0,01*	0,23	<	<	-
Q	- -*	0,06 0,06*	0,01	<	<	0,03	0,04 0,02*	0,31	<	0,02	-
S	- -*	- -*	-	-	<	-	- -*	0,11	-	<	-
U	- -*	- -*	-	-	-	-	- -	<	-	-	-
V	- -*	0,01 0,01*	<	-	-	<	- <*	0,02	-	-	-
During/after pre-treatment											
I	- -*	- <*	<	-	-	0,01	- <*	0,05	-	-	-
J2	- -*	- -*	-	-	-	<	- -*	0,01	-	<	-
J3	- -*	0,01 <*	-	-	-	<	- -*	<	-	-	-
O	- -*	0,10 0,10*	<	-	-	<	- -*	0,19	-	-	-

Sample	Paracetamol	Sulfametoxazol	Metoprolol	Ifosfamid	Erythromycin	Clofibric acid	Bezafibrate	Carbamazepine	Ibuprofen	Diclofenac	Fenofibrate
Drinking water											
A2	--*	--*	-	-	-	-	--*	-	-	-	-
C2	--*	--*	-	-	-	-	--*	<	-	-	-
E2	--*	--*	-	-	-	-	--*	<	-	-	-
N	--*	--*	-	-	-	<	--*	-	-	-	-
P	--*	--*	-	-	-	-	--*	-	-	-	-
W	--*	--*	-	-	-	-	--*	<	-	-	-
STP effluent											
R	--*	--*	0,22	<	0,90	0,07	<< *	0,58	-	0,10	-
T	--*	0,01 0,07*	0,53	-	0,12	-	0,02 0,01*	0,87	-	0,28	-

* = data also obtained with negative ionisation LC/MS/MS
- = not detected
< = below detection limit (0.1 µg/l for paracetamol and fenofibrate, others 0.01 µg/l)

The samples obtained from surface water at the intake of the drinking water plants were sample A, C, E, G, H, J, M, Q, S, U and V.
The samples obtained from treated drinking water were sample A2, C2, E2, N, P, and W.
The samples I, J2, J3 and O were obtained between surface water intake and different stages during the drinking water treatment process.
The samples R and T were obtained from the effluent of sewage treatment plants namely sample R and sample T.

From table 3 it can be seen that carbamazepine was detected in the highest concentrations in surface water, up to 0.31 µg/l.
During drinking water treatment the concentrations in water are reduced considerably. In drinking water no pharmaceuticals were observed or the concentrations were below the detection limit.
The highest concentrations were observed in samples R and T, the effluents of sewage treatment plants. The concentrations observed varied from below the detection limit up to 0.53 µg/l, 0.87 µg/l and 0.90 µg/l for metoprolol, carbamazepine and erythromycin, respectively.
Of the pharmaceuticals investigated, carbamazepine is most predominantly present in surface water and in sewage treatment plants. Sulfamethoxazol and clofibric acid have also been detected frequently.
Ifosfamide and fenofibrate have not been detected in concentrations above the detection limit in either drinking water, surface water or STP effluent.
In drinking water only traces of clofibric acid and carbamazepine have been detected at levels below the detection limit (< 0.01 µg/l). In addition to the remark of the poor recovery rate, it should be mentioned that the analytical methods of clofibric acid and carbamazepine had sufficiently good performance characteristics.

5 Pharmacology and toxicology

5.1 Some general principles

In order to produce its characteristic effects a pharmaceutical must be present in appropriate concentrations at its sites of action. The absorption, biotransformation and excretion of a drug all involve its passage across cell membranes.
Absorption describes the rate at which a drug leaves the site of administration and the extent to which this occurs. Following absorption the drug is distributed throughout the body fluids. The distribution of a drug is dependent on physiological factors and its physicochemical properties.
Most pharmaceuticals have lipophilic properties so they can easily pass the biological membranes and access their site of action. These lipophilic properties however hinder their elimination from the body (hydrophilic compounds are much faster excreted from the body). In reducing the activity of the compound and eliminating it from the body biotransformation of the pharmaceuticals in the body therefore plays an important role.

Drug biotransformation reactions are classified as either phase I functionalisation (biotransformation) reactions or phase II biosynthetic reactions. Phase I reactions introduce or expose a functional group to the parent compound. Usually phase I reactions consist of oxidation, reduction or hydrolysis, making the component better soluble in water. Phase I reactions generally result in the loss of pharmacological activity, although there are examples of retention or enhancement of activity. Sometimes metabolites are formed which have an altered pharmacological activity.
Phase II reactions lead to the formation of a covalent linkage between a functional group of the parent compound with glucuronic acid, sulfate, glutathione, amino acids or acetate. These highly polar conjugates are generally inactive and are excreted rapidly in the urine and faeces.
Pharmaceuticals are eliminated from the body either unchanged or as metabolites. Excretory organs (lungs excluded) eliminate polar compounds more efficiently than substances with high lipid solubility. Lipid-soluble pharmaceuticals are thus not readily eliminated until they are metabolised to more polar compounds. The kidney is the most important organ for elimination of pharmaceuticals and their metabolites. Via the kidney these compounds are excreted in the urine.
There is evidence that the conjugates (formed in phase II reactions) may be hydrolysed to the parent drug or metabolite through bacteria hydrolases when entering the sewage treatment plants (Hirsch et al., 1999).

5.2 Toxicological aspects of pharmaceuticals

Pharmacological and toxicological aspects of the selected drugs are presented in annex 4.
Chemicals that are developed into drugs must have therapeutic efficacy and be safe. All chemicals, however, have the potential to produce unwanted effects.
In therapeutics a drug typically produces numerous effects, but usually only one effect is the primary goal of treatment. Most of the other effects are referred to as undesirable effects of that drug for that therapeutic indication. Side effects of pharmaceuticals are non-deleterious and include effects such as dry mouth. Toxic (deleterious) effects of drugs may be classified as pharmacological, pathological or genotoxic. Because of the toxic effects it is essential in the development of drugs to select chemicals that have a margin of safety between the dose that produces the desired (therapeutic) effect and the dose that produce undesired (toxic) effects. The margin of safety sometimes is small and as a result toxic effects can then be observed.

However these effects can be accepted, for instance when there is no other cure for the disease.

6 Discussion

Pharmaceuticals in drinking water: a health problem?

Pharmaceuticals, as an essential part of modern human medicine, are resorbed, distributed, metabolised and finally excreted. Although all drugs approved by the government have undergone pharmacokinetic studies, there is still a considerable lack of knowledge about their occurrence and fate in the environment.
The current research project has given a first insight in the situation in the Netherlands.

From annex 4 it can be read that the doses of the selected pharmaceuticals (used in humans) range from 100 mg/day to 4 g/day. Comparing these doses with the concentrations observed in drinking water it can be concluded that the margin between the doses used in therapy and the concentrations in water is large (> 10^6).
Next to this, no direct relation has been observed between the presence of pharmaceuticals in water and effects in humans. The development of allergic or sensitisation reactions has been mentioned as one of the possible effects of exposure to low concentrations of pharmaceuticals. Although for some pharmaceuticals (e.g. paracetamol and sulphametoxazol) exposure to low concentrations can already result in sensitisation a direct relation between the concentration in water and the development of an allergic reaction has until now not been established.
At the low concentrations observed in water it will also be very unlikely that any effect will occur.
Additionally, in the current research pharmaceuticals were only detected in surface water and STP-effluent. In drinking water no pharmaceuticals were detected in concentrations above the detection limit.

Still the presence of pharmaceuticals deserves careful attention. It will be important to have reliable data on the current situation to inform the consumer. In the new EC-Directive on the quality of water intended for human consumption(98/83/EC) article 13 states that adequate and up-to-date information on the water intended for human consumption should be available to consumers. Although officially this will be the task for the member states, the responsibility will probably be forwarded to the water supply companies. It will be important for the water supply companies to have the relevant factual information available to keep the customers' confidence and inform them as good as possible. Therefore data are needed concerning the presence of these compounds in surface water and their removal at treatment.
In addition, the average daily intake for some pharmaceuticals should be considered in relation to the concentrations in water (e.g. caffeine), to provide a more general overview for the consumers.

Aspects that remain unsure are indirect effects on human health. The therapeutic application of antibiotics has resulted in the emergence of multi-resistant bacteria like MRSA. The resistance of bacteria in the environment can be induced already at low levels of antibiotic residues. This may result in the emergence of new multi-resistant bacteria or induce resistance in known pathogenic bacteria that can be transmitted by the aquatic environment. An important question is whether the induction of resistance occurs at the antibiotic levels present in sewage and surface water.

7 Conclusions

- In the Netherlands pharmaceuticals have so far only been detected in surface water and effluent of sewage treatment plants at concentrations which do not exceed 1 µg/l.

- In drinking water no pharmaceuticals were detected in concentrations above he detection limit (usually 0.01 µg/l).

- Of the pharmaceuticals investigated, carbamazepine is most predominantly present in surface water and effluent of sewage treatment plants. Sulfamethoxazol and clofibric acid have been detected frequently as well.

- Carbamazepine was detected in the highest concentrations in surface water, up to 0.31 µg/l. Erythromycin was detected in the highest concentrations in STP effluent, up to 0.90 µg/l.

- Ifosfamide and fenofibrate have not been detected in concentrations above the detection limit in either drinking water, surface water or STP effluent.

- The margin between the doses used in therapy and the concentrations in water is large (> 10^6) and at the concentrations observed in water it will be very unlikely that any effect will occur.

8 Recommendations

- To obtain a profound view on the Dutch situation more data are needed on the occurrence of human pharmaceuticals in small and large surface waters, sewage treatment plants and drinking water.

- For informing the consumer and keeping his confidence it is of importance for the water supply companies to have reliable information on the concentrations present in (drinking) water.

- The analytical methods should be further optimised to improve the performance characteristics and, in this way, gain more certainty on the detected concentrations.

- If no data on occurrence are available, a pharmaceutical can still be important based on data of the produced and prescribed amounts. An analytical method should then be developed or adapted and a further assessment of the risk of the pharmaceuticals and their metabolites should be made.

- Reliable information on the concentrations in the environment will also be important from the point of view of the uncertainties about possible allergy and resistance to antibiotics.

References

Aherne, G.W.; A. Hardcastle; A.H. Nield
Cytotoxic drugs and the aquatic environment: estimation of bleomycin in river and water samples.
J. Pharm. Pharmacol, 42, pp 1-12; (1990)

Aherne, G.W.; J. English; V. Marks
The role of immunoassays in the analysis of microcontaminants in water samples
Ecotoxicology and Environmental safety (9) pp. 79-83 (1985)

Buser, H-R; T. Poiger; M.D. Müller
Occurrence and environmental behavior of the chiral pharmaceutical drug ibuprofen in surface waters and in waste water
Env. Sci. Technol. (33) pp 2529-2535 (1999)

Genderen, J. van; J.A. van Leerdam; A. Noordsij
Inventarisatie en toxicologische evaluatie van organische microverontreinigingen, RIWA 1994;

Genderen, J. van; M.N. Mons; J.A. van Leerdam
Inventarisatie en toxicologische evaluatie van organische microverontreinigingen. Herziening 1999; (in press,1999)

Giuliani, F.; T. Koller; F.E. Würgler; R.M. Widmer
Detection of genotoxic activity in native hospital waste water by the umuC test
Mutation Research (368) pp. 49-57; (1996)

Gool, S. van
Possible environmental effects of antibiotics in animal manure
Tijdschrift voor Diergeneeskunde, pp 8/10 (in Dutch); (1993)

Halling - Sørensen; B., S. Nors Nielsen; P.F. Lanzky; F. Ingerslev; H.C. Holten Lützhøft; S. E. Jørgensen
Occurrence, fate and effects of pharmaceutical substances in the environment-
A review
Chemosphere 36 (2), pp 357-393; (1998)

Hirsch, R.; T.A. Ternes; K. Haberer; K. Kratz
Nachweis von Betablockern und Bronchospasmolytica in der Aquatischen Umwelt
Vom Wasser (87) pp. 263-274; (1996)

Hirsch, R.; T. Ternes; K. Haberer; K. Katz
Occurrence of antibiotics in the aquatic environment
The Science of the total environment (225) pp. 109-118; (1999)

Hirsch R.; T.A. Ternes; K. Haberer; A. Mehlich; F. Ballschwanz; K.L. Kratz
Determination of anitbiotics in different water compartments via liquid chromatography-electrospray tandem mass spectrometry
J. Chrom.A. 815, pp 213-223; (1998)

Holm J.V.; K. Rügge; P.L. Bjerg; T.H. Christensen
Occurrence and distribution of pharmaceutical organic compounds in the ground water downgradient of a landfill (Grinsted, Denmark)
Environ. Sci. Tech. 29(5), pp 1415-1420; (1995)

Kümmerer, K.; K. Steger-Hartmann; A. Baranyai; I. Bürhaus
Prüfung des biologischen Abbaus der Zytostatika Cyclophosphamid und Ifosfamid mit dem Closed Bottle Test (OECD 301)
Zbl. Hygiene (198) pp. 215-225; (1996)

Prösch, J.; W. Puchert
Coffein: Vorkommen in Fließgewässern Mecklenburg-Vorpommerns
Vom Wasser (91) pp. 207-214; (1998)

Richardson, M.L.; J.M. Bowron
The fate of pharmaceutical chemicals in the aquatic environment-A review
J. Pharm. Pharmacol. 37, pp 1 - 12; (1985)

Rogers, I.H.; I.K. Birtwell; G.M. Kruzynski
Organic extractables in municipal wastewater
Water Poll. Res. J. Canada (21) 2 pp. 187-204; (1986)

Sacher, F.; E. Lochow; D. Bethmann; H. Brauch
Vorkommen von Arzneimittelwirkstoffen in Oberflächenwässern
Vom Wasser (90) pp. 233-243; (1998)

Stan, H.; T. Heberer; M. Linkerhägner
Vorkommen von Clofibrinsäure im aquatischen System-Führt die therapeutische Anwendung zu einer Belastung von Oberflächen-, Grund- und Trinkwasser?
Vom Wasser (83) pp. 57-68; (1994)

Steger-Hartmann, T.; K. Kümmerer; J. Schecker
Trace analysis of the antineoplastics ifosfamide and cyclophosphamide in sewage water by two-step solid-phase ext5raction and gas chromatography-mass spectometry
Journal of Chromatography A (726) pp. 179-184; (1996)

Stumpf, M.; T. A. Ternes; K. Haberer; P. Seel; W. Baumann
Nachweis von Arzneimittelrückstanden in Kläranlagen und Fließgewässern
Vom Wasser (86) pp. 291-303; (1996)

Stumpf, M.; T.A. Ternes; K. Haberer; W. Baumann
Isolierung von Ibuprofen-Metaboliten und deren Bedeutung als Kontaminanten der aquatischen Umwelt
Vom Wasser (91) pp. 291-303; (1996)

Stumpf, M.; T.A. Ternes; R.D. Wilken; S.V. Rodrigues; W. Baumann
Polar drug residues in sewage and natural waters in the state of Rio de Janero, Brazil
The Science of the Total Environmnet (225) pp. 135-141 (1999)

Ternes, T.A.
Occurrence of drugs in german sewage treatment and rivers
Water Research 32 (11), pp 3245-3260; (1998)

Ternes, T.A.; M. Stumpf; B. Schuppert; K. Haberer
Simultaneous determination of antiseptics and acidic drugs in sewage and river water
Vom Wasser, (90) pp. 295-309; (1998)

Waggott, A.
Trace organis substances in the river Lee (Great Brittain).
Chem. Water Reuse, Vol. 2, pp. 55-99, 1981.

Watts C.D., M. Crathorne; M. Fielding; C.P. Steel
Identification of non-volatile organics in water using field desoprtion mass spectrometry and high performance liquid chromatography.
In: Analysis of organic micropollutants in water
Ed, G. Angelet, A. Brørseth, 1983, pp 120-131.

Annex 1.
Occurrence of pharmaceuticals in surface and drinking water

Compound or breakdown product	Therapeutic use	Occurrence (ng/l)		Reference
		Surface water range or average (max)	Drinking water range or average (max)	
Acetylsalicylic acid	Antiinflammatory drug	d.l.[m] (340)		Ternes (1998)
Betaxolol	Betablocker	n.d[m] (28) 6[m] (9)		Ternes, 1998 Hirsch *et al.*, 1996
Bezafibrate	Lipid regulating agent	<10 - 22 (2xdetected) 350[m] (3100) <25 - 380 100[m] (250) 25	27 (1 of 25 samples > dl)	AWBR, ARW Ternes, 1998 Stumpf, 1996 Stumpf, 1998 Stumpf *et al.* (1999)
Biphenylol	Antiseptic	23[m] (250)		Ternes *et al.*, 1998
Bisoprolol	Betablocker	6 (124) d.l.[m] (2900)		Hirsch, 1996 Ternes, 1998
Bleomycine	Antineoplastic agent	<5 - 17	<5-13	Aherne, 1990
Caffeïne	Psychomotoric stimulant	50 - 1000 10 - 100		Prösch, 1998 RIWA, in press, RIWA, 1994
Carazolol	Betablocker	d.l.[m] (110) d.l.[m] (121)		Ternes, 1998 Hirsch *et al.*, 1996
Carbamazepin	Antiepileptic	250[m] (1100) 1000 <20 - 170; P90:165 (300) 10 - 100		Ternes, 1998 Sacher *et al.*, 1998 AWBR, ARW
Chloramphenicol	Antibiotic	d.l.[m] (60)		Hirsch *et al.*, 1999
Chloortetracyline	Antibiotic	(150)		Richardson,1985
Chlorophene	Antiseptic	11[m] (96)		Ternes *et al.*, 1998
Clarithromycin	Antibiotic	d.l.[m] (260)		Hirsch *et al.*, 1999
Clenbuterol	β_2-sympathomimetic	d.l.[m] (50)		
Clofibric acid	Lipid regulating agent	P90:20-33 (24-37) 7-180 19-222 60[m] (260) 66[m] (550) 20	1 (70) 10 - 165	ARW, AWBR Stumpf, 1996 Stan, 1994 Stumpf, 1998 Ternes, 1998 Stumpf *et al.* (1999)
Dextropropoxyphene	Analgetic	~ 1000		Richardson, 1985
Diclofenac	Analgetic/ antirheumatic	15-489 200[m] (500) 150[m] (1200) <20 - 230 (250) 60	2[m] (6)	Stumpf, 1996 Stumpf, 1998 Ternes, 1998 AWBR, ARW Stumpf *et al.* (1999)

Compound or breakdown product	Therapeutic use	Occurrence (ng/l)		Reference
		Surface water range or average (max)	Drinking water range or average (max)	
Dimethylamino-phenazone	Antiinflammatory drug	d.l.^{m} (340)		Ternes, 1998
Doxycycline	Antibiotic	3690		Römbke, 1996
Erythromycin	Antibiotic	~ 1000 70 - 1700 0.15^{m} (1700)		Watts, 1983 Ternes, 1998 Hirsch *et al.*, 1999
Fenofibric acid	Lipid lowering agent	<5 - 172 45$^{m)}$ (280)	1 x detected > dl	Stumpf ,1996 Ternes, 1998
Fenoterol	β_2-sympathomimetic	d.l.^{m} (61) d.l.^{m} (8)		Ternes, 1998 Hirsch *et al.*, 1996
Gemfibrozil	Lipid lowering agent	<5 - 190 5^{m} (250) 52^{m} (510) <5 - 27 / P90:37 (60)		Stumpf, 1996 Stumpf, 1998 Ternes, 1998 ARW, AWBR
Gentisic acid	Antiinflammatory drug	d.l.^{m} (1200)		Ternes, 1998
Hydroxy-ibuprofen	Breakdown product	60^{m} (340)		Stumpf, 1998
Ibuprofen	Analgetic/ antirheumatic	<5 - 36 6 - 139 20^{m} (140) 70^{m} (530) 1.5 - 7.8 10	(1^{m}) (3)	ARW, AWBR Stumpf 1996 Stumpf 1998 Ternes, 1998 Buser *et al.* 1999 Stumpf *et al.* (1999)
Indometacin	Analgetic/ antirheumatic	<5 - 121 40^{m} (200) <5 - 20 (1 x detected)		Stumpf 1996 Ternes, 1998 ARW, AWBR
Ketoprofen	Antiinflammatory drug	d.l.^{m} (120)		Ternes 1998
Metoprolol	Betablocker	31 (1540) 45^{m} (2200)		Hirsch *et al.*,1996 Ternes, 1998
Metamizol	Analgetic			
Methotrexate	Antineoplastic agent	<6		Aherne, 1985
Nadolol	Betablocker	d.l.^{m} (9)		Hirsch *et al.*, 1996
Naproxen	Antiinflammatory drug	30^{m} (90) 70^{m} (390) 10		Stumpf , 1998 Ternes, 1998 Stumpf *et al.* (1999)
Oxytetracycline	Antibiotic	10 6700		Römbke, 1996 Richardson, 1985
Phenazon	Antiinflammatory	P90:200 24^{m} - (950)		ARW, AWBR Ternes, 1998
Phenacetin	Antiinflammatory	74 (1 x detected)		ARW, AWBR
Propranolol	Betablocker	(98) 12^{m} (590)		Hirsch *et al.*, 1996 Ternes, 1998
Roxithromycin	Antibiotic	<dl - 550 190 (1 x detected)		Ternes, 1998 Hirsch, 1998
Salbutamol	β_2-sympathomimetic	d.l.^{m} (35)		Ternes, 1998

Compound or breakdown product	Therapeutic use	Occurrence (ng/l)		Reference
		Surface water range or average (max)	Drinking water range or average (max)	
Salicylic acid	Antiinflammatory drug	25[m] (4100)		Ternes, 1998
Squalene		~ 1000		RIWA, 1999 in press
Sulphamethazine	Antibiotic	d.l.[m] (160)		Hirsch *et al.*, 1999
Sulphamethoxazol	Antibiotic	~ 1000 40 - 150 d.l.[m] (470)		Watts, 1983 Ternes, 1998 Hirsch *et al.*, 1999
Terbutalin	Bronchospasmolitikum	d.l.[m] (9)		Hirsch *et al.*, 1996
Tetracycline	Antibiotic	2900 1000		Richardson, 1985 Watts, 1983
Theophylline	Psychomotor stimulant	~ 1000		Watts, 1983 RIWA, in press
Timolol	Betablocker	d.l.[m] (10) 6[m] (10)		Ternes, 1998 Hirch *et al.*, 1999
Trimethoprim	Antibiotic	120		Hirsch, 1998

m = median value
dl = detection limit

Annex 2.
Occurrence of pharmaceuticals in sewage effluent (median and maximum concentrations).

Compound	Concentration in ng/l	Reference
Acetaminophen	d.l.^{m} (6000)	Ternes (1998)
Acetylsalicylic acid	~1000 < 50 - 1510 220^{m} (1500)	Richardson & Bowron (1985) Stumpf (1996) Ternes (1998)
Betaxolol	57^{m} (190)	Ternes (1998)
Bezafibrate	< 250 - 4600 2200^{m} (4600) 1100	Stumpf *et al.* (1996) Ternes, 1998 Stumpf *et al.* (1999)
Biphenylol	30^{m} (2600)	Ternes *et al.*, 1998
Bisoprolol	57^{m} (370)	Ternes (1998)
Bleomycin	10-20	Aherne *et al.* (1990)
Caffeïn	~1000 20 - 292	Richardson & Bowron (1985) Rogers *et al.* (1986)
Carbamazepine	2100^{m} (6300)	Ternes (1998)
Carazolol	d.l.^{m} (120)	Ternes (1998)
Chloramphenicol	d.l.^{m} (560)	Hirsch *et al.*, 1999
Chlorophene	50^{m} (710)	Ternes *et al.*, 1998
Clarithromycin	d.l.^{m} (240)	Hirsch *et al.*, 1999
Clenbuterol	d.l.^{m} (80)	Ternes (1998)
Clofibric acid	< 50 - 1560 360^{m} (1600) 120^{m} (1200)	Stumpf *et al.* (1996) Ternes (1998) Stumpf *et al.* (1999)
Cyclophosphamid	146 (treated hospital effluent from STP) d.l.^{m} (20)	Steger-Hartmann (1996) Ternes (1998)
Diazepam	d.l.^{m} (40)	Ternes (1998)
Diclofenac	< 50 - 1600 810^{m} (2100) 400^{m} (1500)	Stumpf *et al.* (1996) Ternes (1998) Stumpf *et al.* (1999)
Dimethylaminophenazone	d.l.^{m} (1000)	Ternes (1998)
Erythromycin-H_2O	2500^{m} (6000)	Hirsch *et al.*, (1999)
Fenofibrate	d.l.^{m} (30)	Ternes (1998)
Fenofibric acid	< 50 - 1200 380^{m} (1200) 50^{m} (750)	Stumpf *et al.* (1996) Ternes (1998) Stumpf *et al.* (1999)
Fenoterol	d.l.^{m} (60)	Ternes (1998)
Gemfibrozil	< 50 - 1460 400^{m} (1500) 400^{m} (1500)	Stumpf *et al.* (1996) Ternes (1998) Stumpf *et al.* (1999)
Gentisic acid	d.l.^{m} (590)	Ternes (1998)
Ibuprofen	3400 370^{m} (3400) 2-81 600^{m} (3500)	Stumpf *et al.* (1996) Ternes (1998) Buser *et al.* (1999) Stumpf *et al.* (1999)
Hydroxy-ibuprofen	5960	Stumpf *et al.* (1998)
Ibuprofen-COOH	260	Stumpf *et al.* (1995)
Ifosfamide	d.l.^{m} (2900) 24 (treated hospital effluent from STP)	Ternes (1998) Steger-Hartmann (1996)

Compound	Concentration in ng/l	Reference
Indometacin	< 50 - 520 270[m] (600) 50[m] (1000)	Stumpf *et al.* (1996) Ternes (1998) Stumpf *et al.* (1999)
Ketoprofen	< 50 - 380 200[m] (300) 150[m] (650)	Stumpf *et al.*(1996) Ternes (1998) Stumpf *et al.* (1999)
Methaqualone	~1000	Richardson & Bowron (1985)
Methotrexate	~1000	Aherne & English (1985)
Metoprolol	730[m] (2200)	Ternes (1998)
Nadolol	25[m] (60)	Ternes (1998)
Naproxen	300[m] (520) 600[m] (2000)	Ternes (1998) Stumpf *et al.* (1999)
Phenazone	160[m] (410)	Ternes (1998)
Propanolol	170[m] (230)	Ternes (1998)
Roxithromycin	680[m] (1000)	Hirsch *et al.*, 1999
Salbutamol	d.l.[m] (170)	Ternes (1998)
Salicylic acid	d.l.[m] (140)	Ternes (1998)
Sulfomethoxazole	400[m] (2000)	Hirsch *et al.*, 1999
Terbutalin	d.l.[m] (120)	Ternes (1998)
Timolol	d.l.[m] (70)	Ternes (1998)
Trimetroprim	320[m] (660)	Hirsch *et al.*, 1999

m = median value
dl = detection limit

Annex 3.
Pharmaceuticals and their (estimated) log Kow values

Pharmaceutical	CAS nr.	Log Kow
Acetyl salicylic acid	50-78-2	1.02
Amitriptyllin[a]		4.72
Ampicyllin[a]	69-53-4	1.35*
Bezafibrate	41859-67-0	4.25•
Biphenylol		3.6•
Bisoprolol	66722-44-9	1.83 (1.87*)
Bleomycin	11056-06-7	0•
Caffeïn	58-08-2	0.07
Carbamazepin	298-46-4	2.45
Chlorohexidin[a]	55-56-1	4.85
Chlorotetracyclin	57-62-5	-0.93 (-1.47 hydrochloride)
Clofibrate[a]	637-07-0	3.62
Clofibric acid		2.8
Codeïne phosphate[a]	52-28-8	-1.01
Cyclophosphamid	50-18-0	0.63
Dextropropoxyphen[a]	469-62-5	4.2• (1.5 hydrochloride)•
Diclofenac	15307-86-5	4.4* • (1.1 sodium acid) •
Dimethylaminophen-azon		0.18
Doxycyclin	564-25-0	-1.36 (.0.02*)
Erythromycin[a]	114-07-8	0.65 (2.5*)
Erythromycin-H2O		< 1•
Fenofibrate	49562-28-9	5.19
Fenofibric acid		2.9•
Gemfibrozil		3.9
Gentisic acid		0.4
Hydroxy-ibuprofen		3.1•
Ibuprofen[a]	15678-27-1	3.68
Ifosfamide[a]	3778-73-2	0.97 (0.86*)
Indomethacin	53-86-1	4.18• (4.27*)
Meprobamate[a]	57-53-4	0.28 (0.7)
Metamizol	68-89-3?	0•
Methotrexate	59-05-2	-1.28 (-1.85*)
Methyldopa[a]	209-089-2	-2.09
Metoprolol	56392-17-7	1.69, 2.3 (1.88*)
Metrodinazol[a]	443-48-1	-0.2
Naproxen[a]	22204-838-7	2.8•
Olaquindox	23696-28-8	-2.13
Oxytetracyclin	79-57-2	-0.9*
Paracetamol	103-90-2	0.27 (0.46*)
Phenacetin	62-44-2	1.58
Phenazon	60-80-0	0.38 (0.3)
Propanolol		3.0 (dis. < 0)
Roxithromycin	80214-83-1	0.39
Squalene	111-02-4	4.7•
Sulphalazin[a]	599-79-1	3.81
Sulphametoxazole[a]	723-46-6	0.89 (0.49*)
Tetracyclin[a]	60-54-8	-1.8 (-1.3*)
Theophyllin	58-55-9	-0.06
Trimethoprim	738-70-5	0.48

Tolbutamide[a]	64-77-7	2.49
Tylosin	1401-69-0	2.10 (1.63*)

* = from literature
• = estimated
other data are from several sources without references (e.g. Internet)

m = median
a = data are available, indicating that this pharmaceutical is less biodegradable

Annex 4
Pharmacological and toxicological aspects of the selected drugs

For the evaluation of the pharmacological and toxicological aspects of the selected drugs the greater part of the relevant information was obtained from Goodman and Gilman's "The pharmacological basis of therapeutics" (J.G. Hardman et al., eds., ninth edition, 1996), "Sax's Dangerous properties of industrial materials" (R.J. Lewis Sr., ed., ninth edition, 1998) and "The Dictionary of Substances and their Effects" (DOSE) (Royal Society of Chemistry, Cambridge, UK, Version April 1999). If relevant, other sources are mentioned in the text.

Pharmacokinetics

In order to produce its characteristic effects a drug must be present in appropriate concentrations at its sites of action. The absorption, distribution, biotransformation and excretion of a drug all involve its passage across cell membranes.

The passage of drugs across biological membranes

The plasma membrane consists of a bilayer of amphipathic lipids, with their hydrocarbon chains oriented inward to form a continuous hydrophobic phase and their hydrophilic heads oriented outward.

Drugs cross membranes either by passive processes or by mechanisms involving the active participation of components of the membrane. In the former, the drug molecule usually penetrates by passive diffusion along a concentration gradient by virtue of its solubility in the lipid layer. Such transfer is directly proportional to the magnitude of the concentration gradient across the membrane and the lipid/water partition coefficient of the drug. The greater the partition coefficient, the higher is the concentration of the drug in the membrane and the faster is its diffusion. After a steady state is attained, the concentration of the free drug is the same on both sides of the membrane, if the drug is a nonelectrolyte. For ionic compounds the steady-state concentrations will be dependent on differences in pH across the membrane, which may influence the state of ionisation of the molecule on each side of the membrane, and on the electrochemical gradient for the ion.

Most biological membranes are relatively permeable to water, either by diffusion or by flow that results from hydrostatic or osmotic differences across the membrane. Such bulk flow of water can carry with it small, water-soluble substances. Most cell membranes permit passage only of water, urea and other small, water-soluble molecules by this mechanism. Such substances generally do not pass through cell membranes if their molecular masses are greater than 100 to 200 Da.

While most inorganic ions would seem to be sufficiently small to penetrate the membrane, their hydrated ionic radius is relatively large. The concentration gradient of many inorganic ions is largely determined by active transport (e.g. Na^+ and K^+). The transmembrane potential frequently determines the distribution of other ions (e.g. chloride) across the membrane.

Absorption of drugs

Absorption describes the rate at which a drug leaves the site of administration and the extent to which this occurs. More important, however, is the extent to which a drug reaches its site of action or a biological fluid from which the drug has access to its site of action. This process is called bioavailability. Common routes of drug administration are the intravenous, subcutaneous and intramuscular routes and oral ingestion. It goes without saying that only the last mentioned route is relevant to the present study.

In addition to the physicochemical factors that affect transport across membranes many variables may influence the absorption of drugs. Absorption from the gastrointestinal tract may be governed by surface area, blood flow to the site of absorption, concentration at the site of absorption and the local alteration of solubility (e.g. aspirin is relatively insoluble in acidic gastric contents).

Distribution of drugs

Following absorption the drug is distributed into interstitial and cellular fluids. The distribution of a drug is dependent on physiological factors and its physicochemical properties. During the initial phase of distribution, dependent on cardiac output and regional blood flow, heart, liver, kidney, brain and other well-perfused organs receive most of the drug during the first few minutes after absorption. Delivery of the drug to muscle, most viscera, skin and fat is slower. The second phase of distribution is determined by the rate at which drugs diffuse into tissues and permeate the cell membrane. Distribution may also be limited by drug binding to plasma proteins, particularly albumin for acidic drugs and α_1-acid glycoprotein for basic drugs. Drugs may accumulate in tissue in higher concentrations than would be expected from diffusion equilibria as a result of pH gradients, binding to intracellular constituents or partitioning into lipid, resulting in an accumulation of the drug. This accumulation may serve as a drug reservoir.

Without considering details it has to be mentioned here that the distribution of drugs to the central nervous system (CNS) is unique, mainly in that entry of drugs into the cerebrospinal fluid and extracellular space of the CNS is restricted.

The potential transfer of drugs across the placenta is important, since drugs may cause congenital anomalies. The view that the placenta is a barrier to drugs is inaccurate. A more appropriate approximation is that the foetus is to at least some extent exposed to essentially all drugs taken by the mother.

Excretion of drugs

Drugs are eliminated from the body either unchanged or as metabolites. Excretory organs, the lungs excluded, eliminate polar compounds more efficiently than substances with high lipid solubility. Lipid-soluble drugs are thus not readily eliminated until they are metabolised to more polar compounds.

The kidney is the most important organ for elimination of drugs and their metabolites. Substances excreted in the faeces are mainly unabsorbed orally ingested drugs or metabolites excreted in the bile and not reabsorbed from the intestinal tract.

Excretion of drugs in breast milk is important, not because of the amounts eliminated, but because the excreted drugs are potential sources of unwanted pharmacological effects in the nursing infant.

Pulmonary excretion is important mainly for the elimination of anaesthetic gases and vapours. Occasionally, small quantities of other drugs or metabolites are excreted by this route.

Classification of carcinogens

The International Agency for Research on Cancer (IARC) classifies the results of carcinogenicity tests that have been carried out in the following categories: (a) sufficient evidence of carcinogenicity, (b) limited evidence of carcinogenicity, (c) inadequate evidence of carcinogenicity and (d) evidence suggesting lack of carcinogenicity. On that basis, four groups of substances are distinguished: (1) human carcinogens, (2) substances that are probably (2A) or possibly (2B) carcinogenic to humans, (3) substances that cannot be placed in a certain category on the basis of the carcinogenicity studies, and (4) substances that are probably not carcinogenic to humans.

There is no adequate evidence for carcinogenicity to humans; paracetamol has been classified by the IARC into group 3.

Sulfamethoxazole

Identity
CAS no.: 723-46-6
Synonyms: 4-amino-N-(methyl-3-isoxazolyl)benzenesulfonamide; N'-(5-methyl-3-isoxazolyl)sulfanilamide; 5-methyl-3-sulfanilamidoisoxazole; 3-(*p*-aminophenylsulfonamide)-5-methylisoxazole; sulfisomezole; sulfamethoxizole; Gantanol; Sinomin
Molecular formula: $C_{10}H_{11}N_3O_3S$

Use
Sulfamethoxazole is an antibacterial and antipneumocytic agent. In the US, UK and most Western European countries, sulfamethoxazole is available in combination with trimethoprim (5:1 ratio sulfamethoxazole : trimethoprim) called co-trimoxazole. It is available as tablets, injections and mixtures.
Sulfamethoxazole is usually administered orally and employed for both systemic and urinary tract infections. The dosage of sulfamethoxazole for children is 50 tot 60 mg/kg initially, followed by 25 to 30 mg/kg morning and evening thereafter. The dosage for adults with mild infections is 2 g, followed by 1 g every 12 hours. For severe disease, the initial dose is 2 g and then 1 g every 8 hours.

Pharmacokinetics
The sulfonamide drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and cure of bacterial infections in human beings. Sulfonamides have a wide range of antimicrobial activity against both gram-positive and gram-negative bacteria. The sulfonamides may be classified into three groups on the basis of the rapidity with which they are absorbed and excreted: (1) agents absorbed rapidly and excreted rapidly, (2) agents absorbed very poorly when administered orally and hence active in the bowel lumen, and (3) long-acting sulfonamides which are absorbed rapidly but excreted slowly. Another group of sulfonamides is employed mainly for topical use. Sulfamethoxazole belongs to group 1. The sulfonamides are structural analogs and competitive antagonists of para-aminobenzoic acid (PABA) and thus prevent normal bacterial utilisation of PABA for the synthesis of folic acid.
In humans, the half-life of sulfamethoxazole is approximately 9 hours whether administered alone or in combination with trimethoprim. Excretion is via the urine with complete elimination within 96 hours. In humans N(4)-acetylsulfamethoxazole is the major metabolite. Minor metabolites include sulfamethoxazole-N'-glucuronide, sulfamethoxazole-N(2)-glucuronide and hydroxysulfamethoxazole. Tissue distribution studies in rats showed high concentrations in kidneys, lung, liver, spleen and brain. The rate of elimination of the drug from most tissues paralleled that from the blood.
Sulfamethoxazole readily crosses the placenta. Administration of the drug to pregnant women in doses of 29.6 and 127.7 µg/ml gave foetal concentrations of 5.1 and 14.8 µg/ml, respectively. Peak concentrations were reached in 10 hours.

Toxicity, adverse effects
Sulfamethoxazole has a moderately acute toxicity via the oral route; LD_{50}s range from 2650-3660 mg/kg in mice to 6370 mg/kg in rats.
In humans, adverse effects include nausea, vomiting, anorexia and diarrhoea. Hypersensitivity reactions include rashes, photosensitivity reactions, exfoliative dermatitis, toxic epidermal necrolysis and erythema nodosum. Renal and blood disorders have also been reported.

Sulfamethoxazole induced neither chromosomal aberrations in human lymphocytes *in vitro*, nor sister chromatid exchanges in human fibroblasts *in vitro*.
Based on the fact that so far no adequate evidence for carcinogenicity to humans and only limited evidence for carcinogenicity to animals has been obtained, sulfamethoxazole has been classified into the IARC group 3.

Erythromycin

Identity
CAS no.: 114-07-8
Synonyms: Erythromycin-A, Abboticin; ERYC; Dotycin; Pantomicina; Robimycin; oxacyclotetradecane, erythromycin deriv.
Molecular fromula: $C_{37}H_{67}NO_{13}$

Use
Erythromycin is an orally effective antibiotic. The drug is one of the macrolide antibiotics, so called because they contain a many-membered lactone ring to which are attached one or more deoxy sugars.
Erythromycin is usually bacteriostatic, but it has been shown to be bactericidal in high concentrations against very susceptible organisms. The drug inhibit protein synthesis by binding reversibly to 50 S ribosomal subunits of sensitive micro-organisms. Erythromycin has been shown to interfere with the binding of chloramphenicol, which also acts at this site.
The usual dose of erythromycin for adults ranges from 1 to 2 g per day, in equally divided and spaced amounts, usually given every 6 hours. Daily doses of erythromycin as large as 8 g orally, given for 3 months, have been well tolerated. The oral dose for children is 30 to 50 mg/kg per day, divided into four portions. This dose may be doubled for severe infections.

Pharmacokinetics
Erythromycin base is incompletely but adequately absorbed from the upper part of the small intestine. It is inactivated by gastric acids and the drug is thus administered as enteric-coated tablets or as capsules containing enteric-coated pellets that dissolve in the duodenum. Peak concentrations in plasma are only 0.3 to 0.5 μg/ml, 4 hours after oral administration of 250 mg of the base, and are 0.3 to 1.9 μg/ml after a single dose of 500 mg. Erythromycin diffuses readily into intracellular fluids, and antibacterial activity can be achieved at essentially all sites except the brain and central nervous system. Only 2% to 5% of orally administered erythromycin is excreted in active from in the urine. The antibiotic is concentrated in the liver and is excreted as the active form in the bile. The plasma elimination half-life of erythromycin is approximately 1.6 hours.

Toxicity, adverse effects
Erythromycin is moderately toxic after ingestion. Oral LD_{50}s range from 3000 mg/kg in rats to 9000 mg/kg in hamsters. In humans no toxic effects on liver function, on the formed elements of the blood or in urinary clinical chemistry have found following administration (by unknown route) of 200 mg erythromycin per day for 7-10 days. However, teratogenic and reproductive effects have been found after subcutaneous administration of 50 mg/kg to female rats.
Serious untoward effects are only rarely caused by erythromycin. Cholestatic hepatitis is the most striking side effect. The symptoms of this illness (nausea, vomiting, abdominal cramps, followed by jaundice) usually disappear within a few days after cessation of drug therapy and rarely are prolonged.
Data on genotoxicity and chronic toxicity are not available.

Metoprolol

Identity
CAS no.: 37350-58-6
Synonyms: CGP 2175; H 93/26; (±)-1-(4-(2-methoxyethyl)phenoxy)-3-((1-methylthyl)amino)-2-propanol
Molecular formula: $C_{15}H_{25}NO_3$

Use

Metoprolol is a β_1-selective adrenergic receptor antagonist. This drug inhibit the interaction of norepinephrine, epinephrine and other sympathomimetic drugs with adrenergic receptors. Norepinephrine is the transmitter of most sympathetic postganglionic fibers and of certain tracts in the central nervous system (The sympathetic outflow and the parasympathetic outflow are the two large divisions of the autonomic nervous system. The autonomic nervous system consists of nerves, ganglia and plexuses that provide the innervation to the heart, blood vessels, glands, other visceral organs and smooth muscle.). Based on the fact that epinephrine, norepinephrine and other related agonists are able to regulate various physiological processes in a different way the adrenergic receptors are divided into α and β receptors. Both α and β receptors are further subdivided based on the potency of the agonists mentioned. β_1-Adrenergic receptors predominates in the myocardium. Metoprolol decreases force and rate of contraction and AV nodal conduction velocity. For the treatment of hypertension, the usual initial dose is 100 mg per day.

Pharmacokinetics

Metoprolol is almost completely absorbed after oral administration, but bioavailability is relatively low (about 40%) because of first-pass metabolism. Plasma concentrations of the drug vary widely (up to 17-fold), perhaps because of genetically determined differences in the rate of metabolism. Metoprolol is extensively metabolised by the hepatic monooxygenase system and only 10% of the administered drug is recovered unchanged in the urine. The half-life of metoprolol is 3 to 4 hours. Both pharmacokinetics and pharmacodynamic interactions have been noted between β-adrenergic-blocking agents and other drugs. Aluminium salts, cholestyramine and colestipol may decrease the absorption of β blockers. Drugs such as phenytion, rifampin and phenobarbital, as well as smoking, induce hepatic biotransformation. Cimetidine and hydralazine may increase the bioavailability of metoprolol.

Toxicity, adverse effects

Metoprolol is moderately toxic after ingestion; oral LD_{50}s vary from 1050 mg/kg in mice to 3470 mg/kg in rats.
The most common adverse effects of β-adrenergic antagonists arise as pharmacological consequences of blockade of β receptors. Serious adverse effects unrelated to β-receptor blockade are rare. Human systemic effects by ingestion are cardiac, eye, and behavioural effects. Common manifestations of overdosage are hypotension, bradycardia, prolonged AV conduction times, and widened QRS complexes. The adverse effects on the central nervous system include fatigue, sleep disturbances, and depression. In literature experimental reproductive effects have been described at relatively high oral doses in rats (60 g/kg).
Data on genotoxicity and chronic toxicity are not available.

Clofibrate, fenofibrate, and bezafibrate

Clofibrate, fenofibrate, and bezafibrate are fibric acid derivatives used to lower plasma lipoprotein levels. Clofibrate is the prototype of this class of drugs. It is the ethylester of *p*-chlorophenoxyisobutyrate. From these drugs the toxicological effects of clofibrate have been described extensively; these effects have been reported to a

lesser extent for the chemical analogues fenofibrate and bezafibrate. Based on this and due to the fact that the adverse effects of the individual fibric acid compounds are more or less comparable, in this paragraph only **clofibrate** is reviewed.

Identity
CAS no.: 637-07-0
Synonyms: ethyl-2-(4-chlorophenoxy)-2-methylpropionate; ethyl-clofibrate; 2-(4-chlorophenoxy)-2-methylpropionic acid ethyl ester; 2-(*p*-chlorophenoxy)-2-methylpropionic acid, ethyl ester; ethyl-chlorophenoxyisobutyrate; ethyl α-(*p*-chlorophenoxy)isobutyrate; Amotril; Cinnanizin; Lipamid
Molecular formula: $C_{12}H_{15}ClO_3$

Use
As mentioned clofibrate is used to lower plasma lipoprotein levels. It causes inhibition of cholesterol synthesis and increased excretion of neutral sterols. Although there have been extensive studies in human beings, the mechanism by which triglyceride-rich lipoprotein levels are lowered or HDL levels are raised, remain unclear. Clofibrate is available for oral administration. The usual dose is 2 g per day in divided doses. Clofibrate is rarely used today.

Pharmacokinetics
All of the fibrate drugs are absorbed rapidly and efficiently (>90%) when given with a meal, but less efficiently when taken on an empty stomach. It appears in the plasma as the de-esterfied *p*-chlorophenoxyisobutyric acid, and peak plasma concentrations of the acid are attained within 2 to 4 hours. More than 95% of these drugs in plasma are protein bound, nearly exclusive to albumin. The drugs are widely distributed, and concentrations in liver, kidney, and intestine exceed the plasma level. The fibrate drugs are excreted predominantly as glucuronide conjugates; 60% to 90% of an oral dose is excreted in the urine, with smaller amounts appearing in the faeces.

Toxicity, adverse effects
Clofibrate is moderately toxic after ingestion; oral LD_{50}s vary from 1280 mg/kg in rats to 1650 mg/kg in mice.
Fibric acid compounds usually are well tolerated. Side effects may occur in 5% to 10% of patients. Gastrointestinal side effects are most common (up to 5% of patients). Oral administration of 500 mg clofibrate 4x over 24 hours to 12 healthy women induced an increase in intragastric acidity . No significant change in plasma gastrin concentration was observed. It was concluded that anti-secretory effects and gastrin-induced cell proliferation is unlikely to occur with the use of this drug. Acute reversible renal failure, due to interstitial nephritis, has been reported with the use of clofibrate. Liver biopsies on 40 patients, before and after 3 months clofibrate therapy, demonstrated no significant histological changes of fatty infiltration in 13 patients receiving 500 mg/day. Of 17 patients with distinct fatty degeneration before treatment with 1.5 g per day, six improved, three deteriorated and eight remained unchanged. No adverse effects were observed. About 5000 patients, 72 reported sexual dysfunction, 14 ceased treatment because of impotence. Other side effects include weight gain, headache, dizziness, fatigue, rashes, pruritis, alopecia, anaemia or leucopenia and a flu-like syndrom.
Clofibrate induced hepatic peroxisome proliferation in rodents, associated with enhanced synthesis of peroxisomal marker enzymes (fatty acid β-oxidation enzymes and catalase).
Clofibrate crosses the placenta and into milk. Post-natal increase in liver α-glycerophosphate dehydrogenase has been reported in newborn rats whose mothers were fed clofibrate. Clofibrate administered orally in Wistar rats in a dose of 150 mg/kg per day from day 16-22 gestation caused decreased birthweight and increased liver weight of the young rats and perinatal mortality. In offspring of dams treated during the last week of pregnancy and during lactation increased liver weight was observed in new-born but this disappeared after one week without treatment.

Clofibrate did not induce genotoxic effects in the Amestest, in mouse splenic lymphocytes *in vitro* and in rat bone marrow cells *in vivo*. Chromosomal aberration and sister chromatid exchanges, however, have been observed in human lymphocytes *in vitro*.
The IARC has classified clofibrate into group 3 due to inadequate evidence for carcinogenicity to humans and limited evidence for carcinogenicity to animals.

Ifosfamide

Identity
CAS no.: 3778-73-2
Synonyms: isophosphamide; N,N-bis(β-chloroethyl)amino-N'-O-propylenephosphoric acid ester diamide; N,3-bis(2-chloroethyl)tetrahydro-2H-1,3,2-oxazaphosphorin-2-amine, 2-oxide; 3-(2-chloroethyl)-2-[(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorin-2-oxide
Molecular formula: $C_7H_{15}C_{12}N_2O_2P$

Use
Ifosfamide, an analog of cyclophosphamide, is an antineoplastic agent used to treat solid tumours of the lung, ovary and testis, and for sarcomas and lymphonas. It is a common component of high-dose chemotherapy regimens used with bone marrow or stem cell rescue. The drug usually is infused intravenously over at least 30 minutes at a dose of 1.2 g/m^2 per day for 5 days. Treatment cycles are usually repeated every 3 to 4 weeks.

Pharmacokinetics
In humans ifosfamide has a half-life in plasma of approximately 15 hours, and clearance is biphasic after a single intravenous bolus of 3.8 to 5.0 g/m^2. Clearance from plasma after repeated, lower doses is monoexponential (monophasic) with a half-life of approximately 7 hours. Ifosfamide is extensively metabolised in the liver to active metabolites. At high doses metabolism appears saturated. It is rapidly metabolised in many animal species, in a similar way to cyclophosphamide, to acrolein and, in dogs, the carboxy derivative and 4-ketoisophosphamide. Metabolic activation in humans may be like that of cyclophosphamide, with ring hydroxylation to isophosphamide mustard and acrolein. An intravenous dose is excreted in urine as one or both dechloroethylated metabolite (50%), intact drug (20%) and carboxyisophosphamide (2%). There is a wide interindividual variation.

Toxicity, adverse effects
Ifosfamide is toxic after oral ingestion; LD_{50}s range from 143 mg/kg in rats to 1005 mg/kg in mice.
Toxic effects of treatment involve urinary tract, kidney and central nervous system. The kidney damage is irreversible. Results in rats suggest that renal damage me be due to the formation of toxic metabolites. Central nervous system effects, which may also be due to a metabolite, include encephalopathy with EEG abnormalities, disorientation, confusion, catatonia, coma and occasionally death from central nervous system depression and circulatory collapse. The incidence of encephalopathy is greater after oral than intravenous administration. The contributory role of mesna, with which it is given, is unclear but may be due to chelating properties. Urinary tract toxicity, characterised by signs of cystitis, limits therapeutic doses. Less important side effects are myelosuppressio, nausea, vomiting, alopecia, lethargy, confusion and reversible glycosuria.
Following a dose of 20 mg/kg given intraperitoneally to mice on day 11 of pregnancy, an increased rate of resorption, growth retardation and incidence of hydrocephalus, micromelia, adactyly, syndactyly, kidney ectopia and delayed ossification have been found. Growth retardation alone occurred at a dose of 10 mg/kg.

Ifosfamide caused positive effects in the Amestest with TA100 and TA1535 with metabolic activation and the Drosophila melanogaster sex-linked recessive lethal test. A dose-dependent increase in chromosomal aberrations in Chinese hamster bone marrow cells was found after intraperitoneal administration.
Ifosfamide has been classified into the IARC group 3 due to the fact that no adequate data for carcinogenicity to humans have been obtained so far and the limited evidence for carcinogenicity in animals.

Carbamazepine

Identity
CAS no.: 298-46-4
Synonyms: 5H-dibenz[b.f.]azepine-5-carboxamide; Biston; Stazepin; Tegretal; Telesmin; Timonil
Molecular formula: $C_{15}H_{12}N_2O$

Use
Carbamazepine is used for the medicinal treatment of schizophrenia. It is effective in the therapy of the epilepsies and it is used as analgesic. Carbamazepine is related chemically to the tricyclic antidepressants. It is a derivative of iminostilbene with a carbamyl group at the 5 position; this moiety is essential for potent antiseizure activity. Carbamazepine limits the repetitive firing of action potential evoked by a sustained depolarization. Therapeutic concentrations are reported to be 6 to 12 μg/ml, although considerable variation occurs. Side effects referable to the central nervous system (see below) are frequent at concentrations above 9 μg/ml. Therapy for epilepsy usually is started at a dosage of 200 mg, taken twice daily. Dosage is then increased gradually to 600 to 1200 mg per day for adults and 20 to 30 mg/kg for children. Therapy for trigeminal neuralgia generally is started at a dose of 200 mg per day. This dose may also be increased to a level of 1200 mg per day, if tolerated.

Pharmacokinetics
Carbamazepine is absorbed slowly and erratically after oral administration. Peak concentrations in plasma usually are observed 4 to 8 hours after oral ingestion. The drug distributes rapidly into all tissues. Binding to plasma proteins occurs to the extent of about 75%, and concentrations in the central nervous system appear to correspond to the concentration of free drug in plasma. Plasma half-life of carbamazepine averages between 10 and 20 hours during long-term therapy.
The predominant pathway of metabolism in humans involves conversion to carbamazepine-10,11-epoxide. This metabolite is as active as the parent compound in various animals. The 10,11-epoxide is metabolised further to inactive compounds, which are excreted in the urine principally as glucuronides. Carbamazepine also is inactivated by conjugation and hydroxylation. Less than 3% of the drug is recovered in the urine as the parent compound or the epoxide.

Toxicity, adverse effects
LD_{50}s in rat, guinea pigs, mice and rabbits vary between 920-2680 mg/kg.
Acute intoxication with carbamazepine can result in stupor or coma, hyperirritability, convulsions, and respiratory depression. During long-term therapy, the more frequent untoward effects of the drug include drowsiness, vertigo, ataxia, diplopia, and blurred vision. Gastro-intestinal symptoms include dry mouth, gastric distress and abdominal pain, nausea, vomiting, anorexia and diarrhoea or constipation. Also several blood disorders such as anemia, eosinophilia, leucopenia and leucocytosis, and abnormalities of liver and kidney function have occasionally been reported. Renal failure caused by acute tubular necrosis was reported in a patient taking 400 mg carbamazepine 4 times per day. Photosensitivity and hypersensitivity have been reported as a result of the therapy with carbamazepine.

A study of 48 children born alive to women treated with carbamazepine prenatally showed that the drug is teratogenic from the incidence of craniofacial defects (11%), fingernail hypoplasia (26%) and developmental delay (20%).
A significant dose-dependent increase in chromosomal aberrations but not in sister chromatid exchanges was observed *in vitro*. *In vivo* studies, however, failed to detect any significant increase of chromosomal aberrations or sister chromatid exchanges or any slowing of the cell cycle.
Although carbamazepine is carcinogenic in rats, it is not known to be carcinogenic in human beings.

Ibuprofen

Identity
CAS no.: 15687-27-1
Synonyms: α-methyl-4-(2-methylpropyl)benzeneacetic acid; *p*-isobutylhydratropic acid; 2-(4-isobutylphenyl)propionic acid; Actifen; Brufen; Ibufen; Motrin
Molecular formula: $C_{13}H_{18}O_2$

Use
Ibuprofen is used as an anti-inflammatory, analgesic and antipyretic drug. Ibuprofen is a propionic acid derivative and it is available for sale without a prescription in the United States (only the 200 mg tablets). This is not the case in Europe.
Ibuprofen is supplied as tablets containg 200 to 800 mg. For rheumatoid arthritis and oseoarthritis, daily doses of up to 3200 mg in divided portions may be given. The usual dose, however, is 1200 to 1800 mg. For mild-to-moderate pain the usual dosage is 400 mg every 4 to 6 hours as needed.

Pharmacokinetics
Ibuprofen is rapidly absorbed after oral administration, and peak concentrations in plasma are observed after 1 to 2 hours. The half-life in plasma is about 2 hours. Ibuprofen is extensively (99%) bound to plasma proteins. The drug passes slowly into the synovial spaces and may remain there in higher concentrations as the concentrations in plasma decline. In experimental animals ibuprofen and its metabolites pass easily across the placenta.
The excretion of ibuprofen is rapid and complete. More than 90% of an ingested dose is excreted in th urine as metabolites or their conjugates. The major metabolites are a hydroxylated and a carboxylated compound.

Toxicity, adverse effects
Ibuprofen is moderately toxic after ingestion; the oral LD_{50} in mice and rats is 740 mg/kg and 636 mg/kg, respectively. An oral dose of 6 mg/kg to near-term rats caused foetal ductal constriction of 70% within 1 to 8 hours, 60% dilatation of both ventricles and 120% increase in pericardial fluid. These changes partly disappeared at 24 hours.
Gastrointestinal side effects are experienced by 5% to 15% of patients taking ibuprofen; epigastric pain, nausea, heartburn, and sensitations of "fullness" in the gastrointestinal tract are the usual difficulties. Other side effects of ibuprofen have been reported less frequently. They include thrombocytopenia, skin rashes, headache, dizziness and blurred vision, and, in a few cases, toxic amblyopia, fluid retention, and oedema.
In vitro rat hepatic toxic effects have been observed at a 10-fold therapeutic plasma concentration for 48 hours, as well as impaired gluconeogenesis from lactate after 6 hours at the therapeutic level and 40% inhibition of albumin synthesis after 6 hours exposure to a 5-fold therapeutic level. In an evaluation of hepatic toxicity involving 1468 patients with rheumatoid arthritis and osteoarthritis no aspartate aminotransferase elevation was observed.