Restrictions on the prescribing of dextropropoxyphene (DXP) – effects on sales and cases of fatal poisoning

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Introduction

On June 15, 2001 the Medical Products Agency (the Swedish medicines control agency) introduced restrictions in Sweden on the prescribing of the analgesic agent dextropropoxyphene (DXP). This was done in the light of findings by researchers in forensic medicine showing that 200 individuals per year died due to poisoning where DXP was judged to have caused or contributed to the fatal outcome.[1] The restrictions state that drugs containing DXP – like other narcotic drugs – must be prescribed on a special prescription form.

Since the 1970s medicines containing DXP have been among the most prescribed analgesics in Sweden.[2] In the 1990s there were seven products containing DXP. These comprised three single preparations - Dexofen, Dolotard and Doloxene – which contained DXP as the only active substance, and four combination products - Distalgesic, Dexodon, Doleron, and Paraflex Comp – which also contained other active analgesic components, e.g. paracetamol and salicylate or the muscle relaxant chlorzoxazone.

Aim and hypotheses

The aim of this report is to evaluate the effects of the restrictions with regard to sales of DXP products, number of cases with DXP found in the blood in forensic medicine examinations, number of cases of poisoning where DXP was judged to have caused or contributed to the fatal outcome and the number of cases of poisoning with DXP reported to the Swedish Poisons Information Centre.

From experience in other countries, which have introduced restrictions on the prescribing of DXP, it is reasonable to assume that:

1. sales of DXP products have decreased,
2. the number of deceased persons with DXP in their blood has decreased,
3. the number of fatal cases of poisoning intoxications in which DXP was judged to have caused or contributed to the fatal outcome has decreased and
4. the number of cases of poisoning with DXP reported to the Swedish Poisons Information Centre has decreased following the introduction of the restrictions.

[1] Jonasson & Jonasson 2001
[2] Apoteket AB

Dextropropoxyphene – general background

In the early 1950s there was a medical need for an analgesic product free of the adverse reactions common in the use of narcotic preparations (e.g. morphine). Examples of such adverse effects are increased tolerance, which involves a risk of dependence, and respiratory impairment, which can be life-threatening in over-consumption or in combination with alcohol.

Dextropropoxyphene (DXP) – a completely synthetic morphine preparation – was introduced to the US market in 1957. The new drug instantly became very popular. The American medical journal JAMA wrote for example that unlike morphine and other stronger analgesics DXP does not cause respiratory depression in therapeutic doses. Furthermore, the tendency towards dependence was described as low, toxicity as low and its safety margin as satisfactory.[3]

However, shortly after the introduction of DXP on the American market reports started to be published on its toxicity.[4] The difference between a therapeutic and a toxic dose turned out to be small and the effects of DXP were enhanced if alcohol was combined with medication containing DXP. Several reports concerning the risks of DXP were published in the 1970s and 1980s in many countries, e.g. the US[5], the UK[6], Norway[7] and Denmark[8]. Restrictions on prescribing were introduced in Norway as early as in 1982 and in Denmark in 1988, which resulted in a substantial decrease in the number of cases of poisoning in these countries.[9]

DXP in Sweden

In Sweden the first report about the risks of DXP came in the early 1970s.[10] It contained a warning that DXP may already cause life-threatening poisoning in slight overdoses and that patients using the product may develop dependence. It was also suggested at this time that the market should be 'cleaned up' with regard to DXP. This report was followed by several others reaching the same conclusion, i.e. that great caution should be exercised in prescribing DXP.[11]

From the 1980s, when the discussion on the toxicity of DXP was most intense in the US, UK, Norway, and Denmark, there is no Swedish documentation. The risks of DXP were brought up again

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[3] Kautz 1958
[4] Cann and Verhulst 1960, Hyatt 1962, Querish 1964, Cawood & Thirkettle 1966, McCarthy & Keenan 1964
[5] Sturner et al 1973, Finkle and co-authors 1976, Hudson 1977, Finkle et al 1981, Finkle 1984,
[6] Young & Lawson 1980, Young 1983, Osselton 1984, Meredith 1984, Vale and co-authors 1984, Whittington 1984,
[7] Jöldal & Halvorsen 1982, Teige 1985
[8] Simonsen & Pedersen 1975, Gertinger & Theilade 1983, Schou 1986, Melsen 1987, Kaa & Dalgaard 1987, Kaa & Dalgaar 1989
[9] Segest & Harris 1993, Worm & Steentoft 1994
[10] Grönwall and co-authors 1971
[11] Fahlen 1973, Gunne and co-authors 1976

by the National Poisons Information Centre in the early 1990s.[12] A retrospective survey of mortality statistics showed an increase in DXP-related deaths in the period 1985 to 1990. The results were alarming and the Information Centre pointed out that it was important to study the use and appropriateness of DXP. In 1996 the Information Centre returned with a study showing that DXP dominated the serious cases and fatalities involving overdoses of analgesics.[13] They urged caution in the prescribing of DXP and stressed the need for new guidelines.

During the period 1998 to 2001 extensive research in forensic medicine was presented.[14] This showed that the occurrence of DXP in forensic statistics increased in the 1990s, and that about 200 people had died per year from poisoning in which DXP was judged to have caused or contributed to the fatal outcome (table 1).

Table 1 Fatal poisoning in which DXP was judged to have caused or contributed to the fatal outcome in 1992 to 1999.

	No of cases of DXP poisoning
1992	158
1993	202
1994	181
1995	188
1996	227
1997	224
1998	195
1999	217
Total	1592

Source: Jonasson 2001

Furthermore, it was shown that beside intentional fatal cases of poisoning – which accounted for more than half – there were entirely unintentional deaths in individuals who had probably been affected due to ignorance about the danger of overdosing the medicine or about the danger of consuming alcohol in combination with DXP. In view of the forensic findings, the National Board of Forensic Medicine demanded, as the Swedish Poisons Information Centre had done previously, that attention should be paid to the problem with DXP and that restrictions should be introduced on the prescribing of DXP.[15]

[12] Persson & Irestedt 1993
[13] Torell and co-authors 1996
[14] Jonasson & Jonasson 1999, Jonasson B 2000, Jonasson U 2001
[15] Jonasson & Jonasson 1999

Sales of DXP in Sweden

It was mentioned above that products containing DXP have been among the most widely sold analgesics since the 1970s. Table 2 shows sales in the 1990s.

Table 2 Sales in DDD/t.i.d. of DXP products

the first quarter in the years 1990 to 1999

	Single products	*Combination products*[2]	*Total*
1990:1	2.2	12.1	14.4
1991:1	2.3	11.1	13.5
1992:1	2.6	11.6	14.2
1993:1	2.8	9.4	12.2
1994:1	3.1	10.6	13.7
1995:1	3.6	9.8	13.2
1996:1	4.0	9.4	13.4
1997:1	3.7	7.2	11.1
1998:1	4.4	8.0	12.5
1999:1	4.8	7.9	12.7

[1] The first quarter is shown to enable comparison with 2003

[2] Sales of combination products include Paraflex Comp

Source: Apoteket AB

Total sales remained largely at the same level – on average 13 DDD/t.i.d. (Defined Daily Dose per 1 000 inhabitants per day) – during the 1990s. However the pattern of sales changed over time. While sales of single products more than doubled from 1990 to 1999, sales of combination products decreased by 35 per cent

Steps taken by Swedish authorities

Restrictions on the prescribing of DXP were introduced in Sweden on 15 June, 2001. The process up to this measure taken by the Medical Products Agency (MPA) is similar to that which occurred in Denmark. The Danish restrictions, introduced in July 1988, were preceded by a combination of published study results, showing a large number of cases of fatal DXP poisoning, involvement by individual doctors, who informed the Danish National Board of Health (Sundhedsstyrelsen) over and over about the problem, attention in the mass media and the involvement of politicians.[16]

[16] Jonasson 2001

In Sweden too the publication of forensic study results was followed by considerable mass media attention and involvement by politicians. With reference to the forensic findings a dialogue was started between the Medical Products Agency and the National Board of Forensic Medicine as early as 1998. At this point the mass media had started to show interest in the forensic research results and the problem of DXP poisoning was also discussed in the Swedish Parliament several times in the form of questions for written answers, submission of a motion and an interpellation.[17]

Steps to reduce the risks of DXP were taken gradually. In the spring of 1999 the Medical Products Agency and the National Board of Health and Welfare, against the backdrop of the reports referred to above on DXP poisoning, in co-operation with the National Board of Forensic Medicine and the National Swedish Poisons Information Centre arranged a seminar on analgesics. The aim of the seminar was, among other things, to focus on DXP from a pharmacological, toxicological and a physiological (pain) point of view. This seminar attracted a great deal of attention in the media and the public were asked to be cautious, especially with regard to concurrent use of DXP and alcohol.

In the autumn of 1999 the Medical Products Agency performed an investigation on what steps should be taken in order to reduce the risks of DXP. After hearing experts and other authorities, the Medical Products Agency in August 2000 urged that the manufacturers concerned should amend their SPCs, PILs and labelling by the start of 2001. In the new warnings it should be clearly stated that an overdose of DXP and the combination of alcohol can be life-threatening. The manufacturers were also urged to introduce smaller packages.[18]

Finally in June 2001 prescribing restrictions were introduced, with the effect that a special prescription form used for prescriptions of other narcotic drugs, such as benzodiazepines, should also be used when prescribing products containing DXP. In general the Medical Products Agency recommended a restrictive prescribing of DXP adapted to the needs of the individual and a thorough follow-up of the efficacy of the treatment.[19]

The introduction of restrictions in Sweden has attracted notice in the European Parliament. In the light of the fact that consumption of DXP per capita e.g. in France and in the UK is markedly greater than in Sweden a question was put by the Parliament to the European Commission[20] as to whether the authorities in the other member states are aware of the risks of DXP – and if so, whether they had taken any precautions similar to those in Sweden. The European Commission intends to follow up the outcome of the restrictions in Sweden. Thus, this report is therefore not just of significance for Sweden but for the authorities in other member states will act as well.

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[17] Question 1998/99:600, Motion 1999/2000:v443, Interpellation 1999/2000:355
[18] Medical Products Agency 2000
[19] Press release by Medical Products Agency August 29, 2000 and June 13, 2001

[20] Marit Paulsen asked the European Commission, which answered in May 2003

The study

The aim of the study is to analyse whether any changes have occurred in sales, forensic material or hospitalised cases of poisoning as a result of the restrictions. Data have been collected separately from these three areas (see below). In order to investigate the time before and after the restrictions the study extends over the years 2000 to 2002. To additionally show the development after the introduction of restrictions, data from the first quarter of 2003 have been collected where possible. In order to focus further on certain aspects, comparisons have also been made with data from the 1990s.

Sales data for DXP products

Data on sales of DXP products for the studied period have been received from Apoteket AB and the Medical Products Agency. Sales are presented as DDD/t.i.d. - Defined Daily Dose per 1 000 inhabitants per day.

Data from Forensic Medicine

In order to study the occurrence of DXP in forensic material and the number of cases of poisoning where DXP was judged to have caused or contributed to the fatal outcome, data were collected from two national databases, *RättsBase* and *ToxBase,* linked to forensic medicine and forensic chemistry in Sweden.

The task of *Forensic Medicine* is to study obvious or suspected cases of unnatural death and establish cause of death and manner of death (accidental, suicide, murder or unclear).[21] All cases of death where poisoning is suspected should be referred to Forensic Medicine for further investigation and autopsy, including in cases where a patient has died in hospital. All misusers found dead must also undergo forensic examination. In the latest decade autopsies have been performed in about 20 per cent of all deaths, i.e. in about 18 500 cases per year. Among these, the proportion of cases subjected to forensic

[21] When assessing the manner of death accidental, suicide and unclear the forensic pathologist tries to obtain a picture of the deceased person's own intention to die. The basis for this is taken from the autopsy results, from the forensic chemical analysis and from the police report which describes the particular circumstances of the death. Relatives of the deceased may also be contacted for further information. A case of poisoning is assessed as an *accident* when it is quite clear that the deceased had no intention whatsoever to die. Clear evidence or very strong indications that the deceased's real intention was to die is required for a case to be assessed as *suicide.* In cases where it cannot be decided if the intention of the deceased was to die, the death should be classified as unclear.

autopsy has been stable at about 30 per cent (about 5 600 autopsies per year). This signifies that possible changes in the number of cases in which DXP was judged to have caused or contributed to the fatal outcome in all probability cannot be explained by changes in the number of forensic autopsies.

The post mortem investigations are performed in co-operation with the Department of Forensic Chemistry to a large extent. The task of this department is to measure levels of alcohol, medicines, narcotics and other toxic agents in biological samples, primarily blood, urine and eye chamber fluid. Screening of illegal drugs, such as amphetamine, cannabis and cocaine are requested if the doctor of forensic medicine has reason to believe that any of these drugs might be found in the deceased. Chemical analyses are performed in about 90 per cent of all forensic post mortem investigations.

The studied population is the total Swedish Forensic Medicine autopsy material in the years 2000 to 2002. Certain data from the first quarter of 2003 are also presented in the study. All cases in which measurable amounts of DXP were found in peripheral blood were included in the study. Concurrent findings of alcohol and other drugs are taken into account in the analysis. Concentrations of DXP in the blood are presented as µg/g. Data on causes of death, manner of death and signs of abuse are also analysed.

DXP poisoning is defined, as in previous forensic medicine studies, as all cases in which DXP was found in the blood and the forensic pathologist noted poisoning as the primary or secondary cause of death.[22] DXP poisoning therefore comprises cases where

1. only DXP was found in the blood and was therefore the sole cause of death,
2. DXP and other drugs were found in the blood, but DXP was the sole cause of death,
3. DXP in combination with other drugs was the cause of death,
4. DXP in combination with other drugs contributed to the death or,
5. DXP was found in the blood but did not contribute to the death in any significant way. (Comment: Includes cases of poisoning in which DXP was found in the blood within the therapeutic concentration. The forensic pathologist has assessed the case as a poisoning but has not made any specific statement that DXP contributed to the fatal outcome. This is often the case when the deceased person has several substances in the blood and it is impossible to judge whether DXP contributed to the death or not. There are only a few such cases).

Data from the Swedish Poisons Information Centre

[22] The assessment of the forensic pathologist is based upon results from the autopsy, the forensic chemistry analyses and the summary of the circumstances of the death found in the police report.

The Swedish Poisons Information Centre monitors cases of poisoning in Sweden by collecting three different kinds of data: *medical records*, i.e. reports concerning patients hospitalised due to poisoning, *statistics* on received questions and *spontaneous observations* (within the Centre's advisory activities). In this study, data from the Centre's information from medical records and statistics on questions have been collected.

The Centre receives discharge reports concerning a little more than a third of hospitalised patients treated for poisoning. The strength of these data is mainly that the cases of poisoning can be characterised qualitatively, as they provide, among other things, information on the development of symptoms. Such information is important for the assessment of the risk pattern of the individual case of poisoning. The seriousness of the cases of poisoning is assessed from the actual clinical development of symptoms and does not take into account medical history data on dose taken or concentration in serum.[23]

Discharge reports concerning cases of poisoning with DXP in the period of 2000 to 2002 have been analysed retrospectively. During this period the degree of reporting is estimated to have remained constant. Type of drug (single or combination product), number of cases of poisoning, method, sex distribution and severity were observed. A comparison with data from the period 1991 to 1993 was also made. Cases of poisoning in children below 10 years of age were excluded as these constitute a special category in which serious cases of poisoning are very rare. Only discharge reports in which DXP occurred alone or was assessed as being the most important poison are presented in the study. The combination of DXP and alcohol was included. Each new hospitalisation of a patient results in a new discharge report. Thus, the same patient can be included several times in the study material.

The inquiry statistics from the Swedish Poisons Information Centre do not provide any information on the total number of cases of poisoning in Sweden, but may show certain changes in pattern of poisoning. For this reason these data were included in the study.

[23] Persson and co-authors 1998

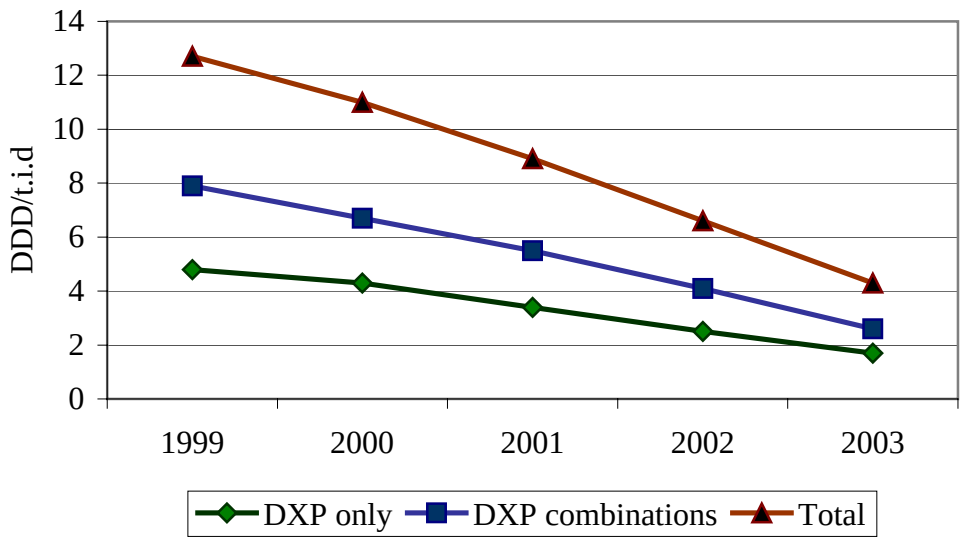
Results and discussion

The aim of this study is to evaluate the effects of restrictions on the prescribing of DXP, i.e. variations during the studied period. The restrictions are assumed to have an impact on sales of DXP products and the number of cases of fatal DXP poisoning and the number of cases of poisoning reported to the Swedish Poisons Information Centre. In this section development during the years 2000 to 2002 is presented separately for these three areas.

Sales of DXP products

In order to investigate if sales were affected by the restrictions, sales in the first three months of the years 1999 to 2003 are presented. As mentioned in the introduction total sales were fairly constant during the 1990s (13 DDD/t.i.d. on average).

Figure 1 Sales of DXP products in the first three months of the years 1999 to 2003.



The study shows that sales decreased gradually during the studied period. In the first quarter of 2003 sales were 66 per cent lower in comparison with the first quarter of 1999. As can be seen in Figure 1, the decrease in sales had already started before the restrictions were introduced, which can probably be explained by the great publicity that the forensic study results brought about in the media in the period from 1998 to 2001. The decrease has continued, however, and sales were halved between the first quarter of 2001 and the first quarter of 2003. The continued decrease is most probably due to the restrictions.

A further factor which may have had effect on sales of DXP is the increased sales of tramadol. Tramadol, a centrally acting analgesic, was introduced on the Swedish market in the mid-1990s. Sales of tramadol have increased continuously and in 2002 stood at 5.7 DDD/t.i.d. It is difficult to know cause and effect in the relation between decreased sales of DXP and increased sales of tramadol. A guess might be that the decreased sales of DXP created a market for tramadol, which was introduced at the same time. This conclusion is based on the assumption that if tramadol had had such an impact as to take market shares from DXP in such a short time, sales of analgesics containing codeine would have been affected as well. This was not the case. Sales of codeine products were constantly about 10 DDD/t.i.d. in the period from 1992 to 2002.

The conclusion is made that sales first were affected by publicity on the forensic studies and later – and above all – by the restrictions. Previous research has shown that campaigns and attention from media, e.g. in the US, only have resulted in a temporary decline in sales of DXP.[24] In order to influence sales with a long-term effect it is highly likely that action by the authorities concerned is necessary.

Forensic medicine studies

The account of forensic medicine studies starts with an analysis of the occurrence of DXP in deceased persons during the period from 2000 to 2002. To evaluate the effects of the restrictions there is also an account for each year separately. If there is a change in the number of cases of DXP poisoning it is also important to investigate if there is any change in the characteristics of those who are poisoned with regard to sex, age and manner of death. For this reason the data in the present study were compared with those from a previous study which comprised all those who died from DXP poisoning in the period from 1992 to 1996.[25] Since alcohol and certain other substances, such as benzodiazepines, have a potentiating effect on DXP[26], those who consume large amounts of alcohol and misusers are more at risk of dying from DXP poisoning. For this reason the presence of alcohol in the blood and comments on abuse in the death certificate are presented separately.

DXP in forensic material and fatal DXP poisoning

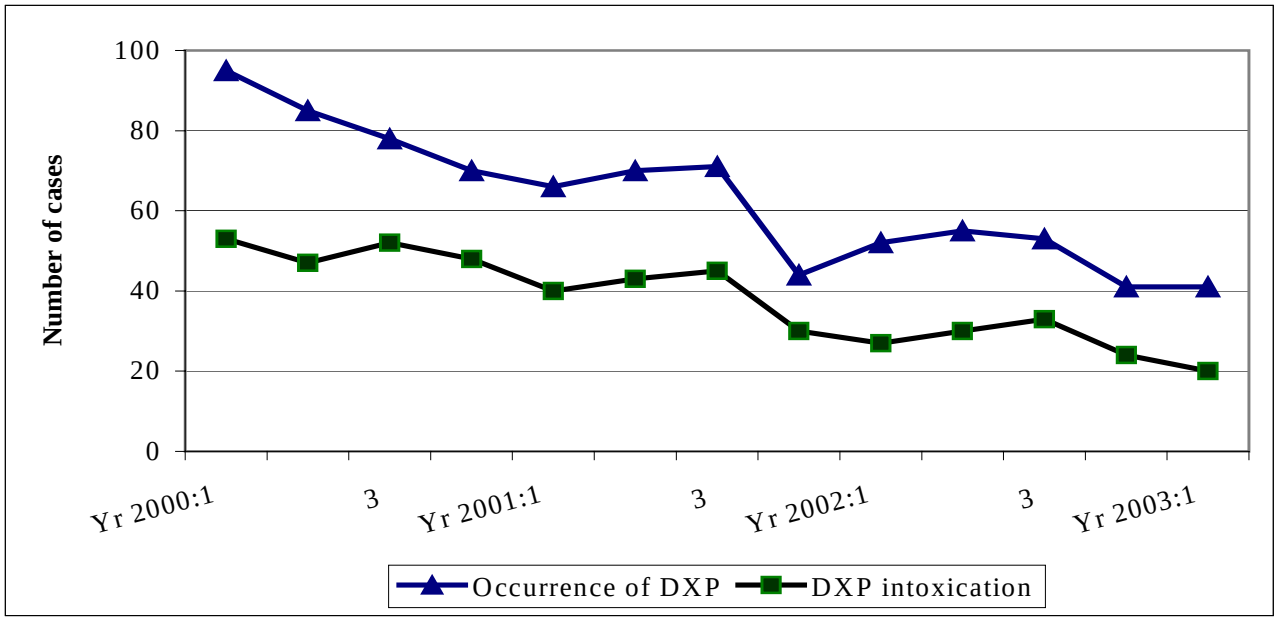
During the years studied, 14 779 blood samples were tested at the department of forensic chemistry. Among these 780 (5.3 per cent) contained measurable levels of DXP. In 472 (61 per cent) of these cases poisoning was judged to be the primary or secondary cause of death (433 and 39 individuals respectively). Of those who were poisoned, 43 per cent were women and 57 men. Those who had died

[24] Soumerai 1989
[25] Jonasson and co-authors 1998

from poisoning were significantly older than those who had died from other causes (54 years as compared with 40 years). Among those who were poisoned, the way in which death occurred was judged as accidental, i.e. according to the judgement of the forensic pathologist the deceased did not have any intention to die, in 66 cases (14 per cent) and as suicide in 255 cases (54 per cent). In the remaining 151 cases (32 per cent) the forensic pathologist could not decide whether it was a case of accident or suicide and therefore these were classified as 'unclear'. There was no significant difference between the separate years with regard to sex distribution, age distribution or distribution of manner of death.

To investigate if the presence of DXP in forensic material and the number of cases of fatal poisoning decreased following the restrictions, each quarter of the studied years is presented in Figure 2. The number of cases can be reported as the number of blood samples analysed per quarter remained constant during the years studied (about 1200 per quarter). This signifies that a change in the number of cases with DXP in the blood or in the number of cases of DXP poisoning probably cannot be attributed to a decrease or increase in the number of analysed blood samples.

Figure 2 Presence of DXP and fatal cases of DXP poisoning in forensic material presented for one quarter of a year for the years 2000:1-2003:1.



[26] Lund & Nielsen 1972, Christensen 1977

The result shows that the number of cases with DXP in the blood continuously decreased during the whole time period as well as the number of cases of DXP poisoning. From the first quarter of 2000 up to the first quarter of 2003 the number of cases with DXP in the blood decreased by 57 per cent, from 95 to 41. The number of cases of DXP poisoning decreased from 53 per quarter to 20 during the same period, i.e. a decrease of 62 per cent.

Just as was the case with sales, the decrease in number of cases with DXP in the blood and the number of cases of DXP poisoning started before the restrictions and then there was a substantial fall during the last quarter of 2001. The number of cases of DXP poisoning per quarter has been reduced by half since the restrictions were introduced (from 45 to 20). It can be noted that there was a weak tendency towards an increase of both variables in 2001, which may indicate that the decrease brought about by publicity in the media was subsiding. When the restrictions were introduced the issue attracted attention again among users as well as subscribers which may have caused the obvious decrease during the last quarter of 2001. It could be guessed that the increase which occurred during the first quarter of 2002 might be explained by a large number of tablets stored at home. Even if doctors in the same period became more cautious in prescribing, patients who wanted DXP products could still take them even if they did not have their prescriptions renewed. The low number of cases of DXP poisoning in the last two quarters (24 and 20) may indicate that such stores have been used up, which in turn may result in a greater impact of the reduced prescribing.

One or more substances in the blood

As mentioned above, patients who were found to have DXP in their blood may have taken another substance or other substances. In the cases assessed as DXP poisoning, death may have been caused by one substance only or by a combination of different substances. Table 3 shows the proportion of deceased persons who had one or more substances in their blood. To investigate if the concentration of DXP in the blood differed between those who had taken one substance and those who had more than one substance, this is presented in Table 3. The concentration in the blood following a therapeutic dose is regarded as being 0.05-0.75 µg/g.[27]

Table 3 Number of deceased persons who had one or more substances in their blood and the concentration of DXP[1].

	Non-poisoning			Poisoning		
	%	(n)	µg/g	%	(n)	µg/g

[27] Druid & Holmgren 1997

Only DXP in blood	25 (76)	0.54	12 (57)	3.42
DXP + alcohol	14 (42)	0.45	16 (77)	4.32
DXP + several other drugs[2]	62 (190)	0.76	72 (338)	2.82

[1] Only the cases in which blood samples were taken from femoral blood (peripheral blood) were included in the calculation of DXP in the blood (288 and 440 individuals respectively)

[2] Including alcohol, in cases where it was found

Table 3 shows that a majority of those who died from poisoning as well as those who died from other causes also had other substances in their blood (62 and 72 per cent respectively). Previous studies[28] have shown that those who die from DXP poisoning are often individuals who take a number of different drugs, findings that are confirmed by these results.

The concentration of DXP in the blood in individuals who died from other causes than poisoning corresponded to a therapeutic dose, whereas the average DXP concentration in those who were poisoned was four to six times higher than the therapeutic dose. There was no difference in DXP concentration between those who had one substance in their blood as compared with those who had more than one substance. Among those who were poisoned, 12 per cent had a DXP concentration lower than 0.75 μg/g. Whether or not DXP had minor significance for the fatal outcome in these cases cannot be established because many factors act together in poisoning, such as individual metabolism and possible development of tolerance.

Comparison of the periods 1992 to 1996 and 2000 to 2002

Because the number of cases of intoxication decreased during the years studied, it is also important to examine if there was any change in the characteristics of the individuals within the group who were poisoned in comparison with previous years. Data from a study investigating the manner of death in those who died from DXP poisoning in the period 1992 to 1996[29] were chosen for comparison. In Table 4 we present the sex and age distribution and the manner of death among those who died from DXP poisoning in the periods 1992 to 1996 and 2000 to 2002.

[28] Finkle 1984

[29] Jonasson and co-authors 1998

Table 4 Distribution of sex, age and manner of death in fatal cases of DXP poisoning in per cent

	Years 1992 to 1996 n=956	*Years 2000 to 2002 n=472*
Sex		
Women	44	43
Men	56	57
Age		
0-19	2	2
20-39	34	15
40-69	51	64
70 yrs and older	13	19
Manner of death		
Accidents	5	14
Suicide	57	52
Unknown	38	34

The results show that the sex distribution of those who died from DXP poisoning was the same for the two studied periods. However, there is an obvious shifting of age distribution. While 64 per cent were over 40 years of age in the period of 1992 to 1996, 83 per cent were over the age of 40 in the period from 2000 to 2002. The number of individuals poisoned in the 20 to 39 age group was reduced by half between these periods. The fact that a larger number of older patients were among those who died from DXP poisoning in the latter period might indicate that doctors had become less inclined to prescribe DXP to younger people. As the sales of DXP have been closely related to age[30] it is also possible that older people had DXP products stored at home to a larger extent than young people, resulting in an early decrease in fatalities in younger people.

Information in the media about the toxicity of a drug can have both positive and negative effects. Individuals who are prone to suicide may be given an impulse to take their lives with the drug, whereas people who are at risk of being victims of involuntary poisoning may become more cautious. It is therefore reasonable to assume that the proportion of suicides resulting from the publicity on the research results and the restrictions would increase in the period 2000 to 2002 as compared with the period 1992 to 1996. Table 5 proves this assumption to be wrong. The proportion of accidental cases

[30] Apoteket AB

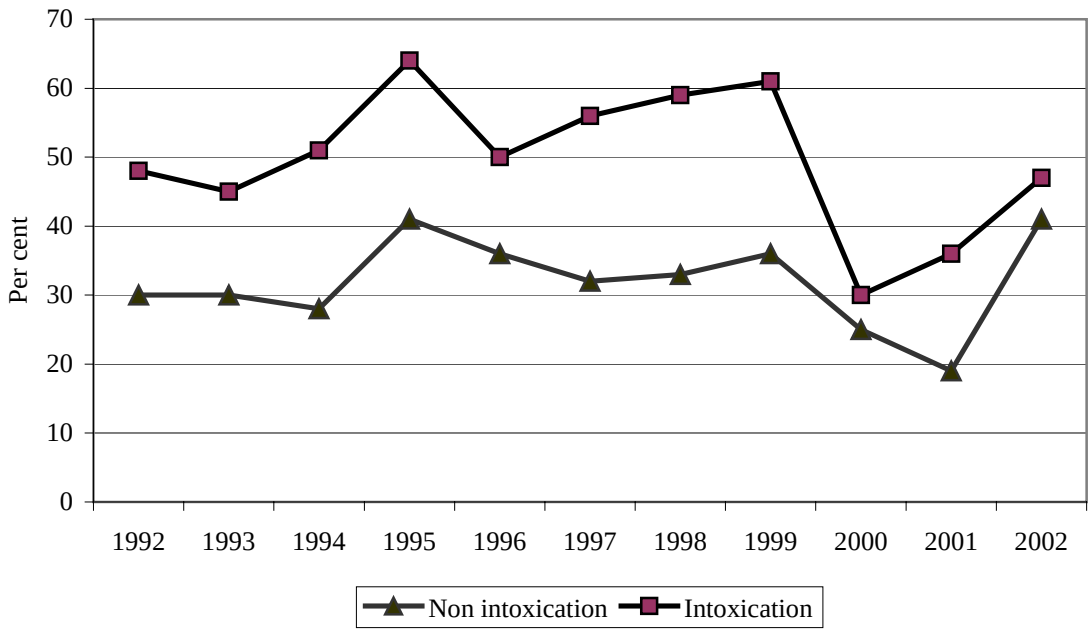
seems to have trebled according to this result. This increase must be regarded as uncertain as it could be explained by an *increased tendency* among the forensic pathologists to assess a DXP intoxication as an accident, rather than the number of accidents previously having been lower. This assumption is based upon a previous study in forensic medicine showing the number of accidents to be under-reported with regard to cases of DXP poisoning.[31] This study was noted in forensic medicine and it is likely that the forensic pathologists' judgement may have been influenced. The number of cases assessed as unclear has decreased slightly but amounts to such a number that it would be difficult to state with any accuracy the total number of people who may have died by accident, i.e. who did not have any intention to commit suicide.

Concurrent presence of DXP and alcohol in blood samples

Because the concurrent consumption of DXP and alcohol involves great risks, the publicity on the forensic research and the actions taken by the Medical Products Agency have focused on disseminating information about these risks. The information in FASS (Swedish equivalent to PDR) and in the patient information leaflet is far clearer that alcohol consumption should be avoided within 24 hours before or 48 hours after intake of DXP. Therefore, it is important to investigate if there has been any change with regard to concurrent presence of alcohol and DXP in the blood of the deceased. In order to have as comprehensive a picture as possible, the analysis was made for all the cases with DXP in the blood in the period from 1992 to 2002 (Figure 3).

[31] Jonasson and co-authors 1999

Figure 3 Number of deceased with DXP in the blood in the period 1992 to 2002 who also had alcohol in the blood.



The results show that a large proportion of the subjects in both groups consumed alcohol concurrently with DXP (on average 32 and 50 per cent respectively). A considerable decrease can be noted for both groups in the years 2000 and 2001, but in 2002 the proportion of subjects with alcohol in the blood increased again. It can be noted that the proportion of subjects with alcohol in the blood in that year was about the same in both groups (41 and 47 per cent respectively). The temporary decrease in 2000 and 2001 can possibly be explained by the extensive publicity in the media in the period 1998 to 2001on the risk of mixing DXP with alcohol. The fact that the proportion increased again could be an example of the assumption that publicity in the media mostly only has temporary effects. Another explanation could be that more 'ordinary' patients treated for pain had changed to alternative drug regimens after the restrictions and that those who still take DXP to a greater extent belong to risk groups, in which concurrent use of alcohol and DXP is more common (misusers and suicidal individuals).

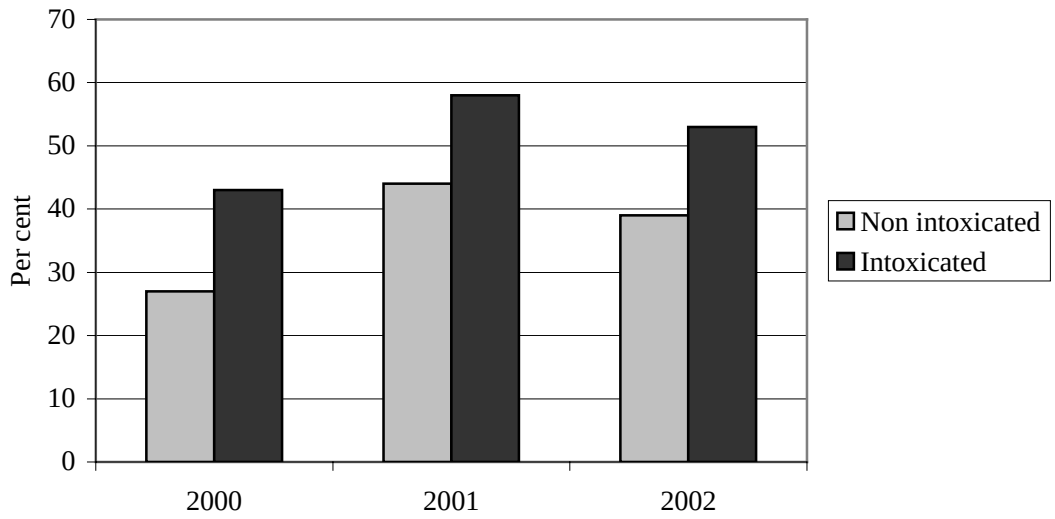
Notes on abuse in death certificates

It has been assumed that a large proportion number of those who die from involuntary DXP poisoning belong to the so-called abuse population, i.e. people who abuse alcohol and/or other, often illegal, substances. However, it has previously been difficult to obtain a correct picture of the extent to which the deceased had been misusers. As an example it was shown in a previous study that only 10 per cent

of those who died from DXP poisoning in 1992 to 1996 had a note on abuse in the death certificates.[32] This was assumed to be a considerable underestimate of the proportion of misusers because previous studies had shown that notes on abuse in death certificates had been under-reported.[33]

In 1999 new routines for the registration of abuse in death certificates were introduced and in Figure 4 we show the number of deceased persons with notes on abuse in the death certificates during the period 2000 to 2002.

Figure 4 Deceased persons with DXP in the blood for which notes on abuse were made in the death certificates (per cent)



Not unexpectedly the results show that a large proportion of those who died from DXP poisoning were noted as misusers (on average 51 per cent). Somewhat surprisingly, this also applied to those who died from other causes (on average 37 per cent). The proportion of cases that had a note on abuse in the death certificate increased significantly from 2000 to 2001 in both groups. On the other hand there was no significant difference between 2001 and 2002. The increase in 2000 and 2001 might be due to the fact that the number of misusers actually increased. However, it seems more likely that the increase reflects the new procedures being put into practice by forensic pathologists to an increasing extent. It is well known that it takes time to implement new procedures. From the previous study we know that only 10 per cent of those who died from DXP poisoning had a note on abuse in their death certificates. It can now be concluded that the introduction of the new procedures led to a considerably more accurate estimate of the number of misusers in forensic material in comparison with ten years ago.

[32] Jonasson and co-authors 1998
[33] Ågren & Jacobsson 1987

Cases of poisoning reported to the Swedish Poisons Information Centre

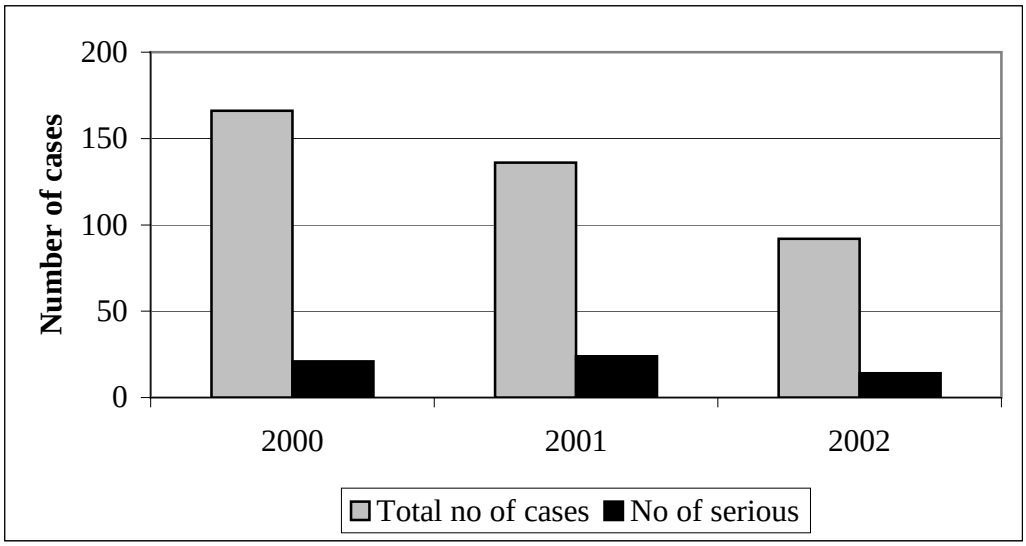
Between 2000 and 2002 a total of 394 medical records were sent to the Swedish Poisons Information Centre in which DXP were judged to be the main agent of poisoning. The number of cases of serious and life-threatening poisoning was on average 15 per cent, which agrees with the result of a previous study.[34] Six individuals died after arrival in hospital and two had hypoxic brain damage. In 217 cases (55 per cent) the poisoning was caused by single preparations (DXP only) and in the rest of the cases by combination products (mainly DXP in combination with paracetamol). The majority of the cases (95 per cent) involved deliberate intoxication[35] or cases where the intent was unclear. Case of acute poisoning as a result of abuse and accidents in connection with medication were rare. Medication errors did not result in serious symptoms in this material, with one exception. A general observation is that many of the patients, irrespective of the origin of the poisoning, either had had a chronic condition with pain or a history of abuse. It can be noted that one single patient had a record of 26 healthcare episodes in the studied period. In the material as a whole 63 per cent were women, but among young people under 20 years of age almost all who overdosed were women. In this group most cases involved what are referred to as acts of impulse.

In order to investigate if the number of cases of DXP poisoning reported to the Swedish Poisons Information Centre had changed in connection with the restrictions, the number of cases are presented per year in the three-year period 2000 to 2002 (Figure 5).

[34] Torell and co-authors 1996

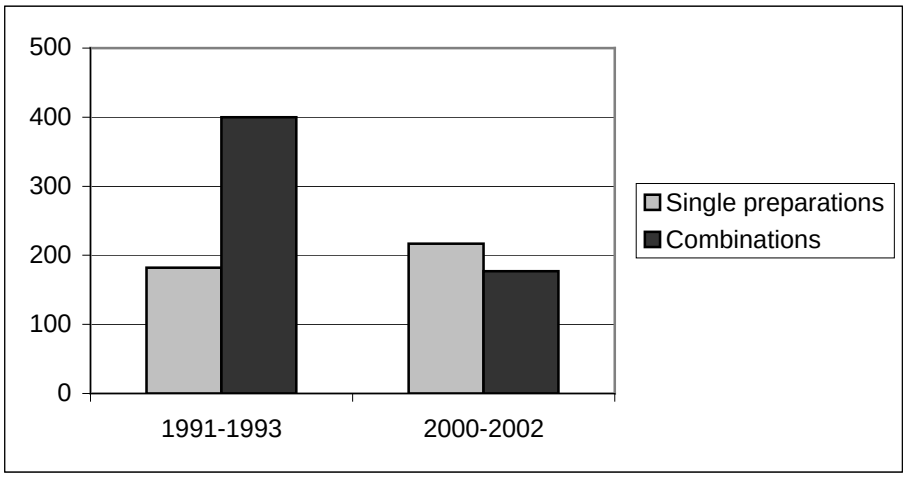
[35] Considering the forensic assessment of the manner of death it is important to point out here that the definition used by the Swedish Poisons Information Centre *'intentional overdose'* is not synonymous with an intention to die

Figure 5 Number of hospital records concerning cases of DXP poisoning received by the Swedish Poisons Information Centre 2000 to 2002



In Figure 5 it is evident that the number of discharge reports decreased gradually during the three-year period (by 45 per cent in total). It is reasonable to assume that this decrease is an effect of the restrictions. No compilation of data has been made for the end of the 1990s. Thus, it is not possible from this study to demonstrate if the decrease in number of hospital records, like the decrease in sales of DXP and the number of fatal cases of DXP poisoning, started even before the restrictions were introduced. What can be examined, however, is if the number of discharge reports has changed in comparison with the beginning of the 1990s. The discharge reports for 1991-1993 and 2000-2002 are therefore shown in Figure 6.

Figure 6 Cases of poisoning with DXP in the periods 1991 to 1993 and 2000 to 2002

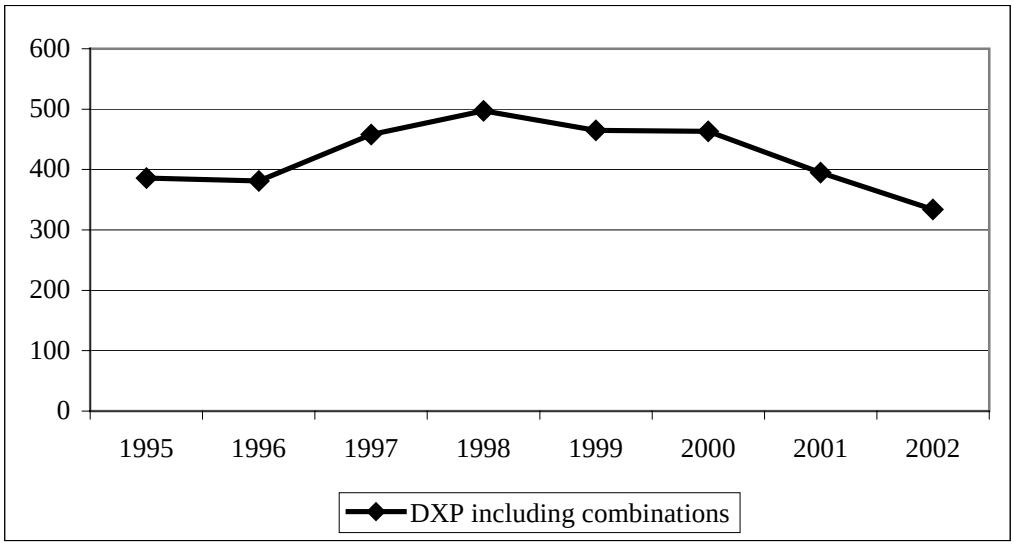


The study shows that the total number of discharge reports concerning poisoning with DXP products in the period 2000 to 2002 was lower in comparison with the period 1991 to 1993. Between 1991 and 1993, 582 discharge reports were received as compared with 394 between 2000 and 2002, a decrease of 32 per cent. As can be seen in Figure 6, cases of poisoning with combination products dominate in 1991 to 1993 whereas poisoning with single preparations occurred to a greater extent in 2000 to 2001. This probably reflects the decreased sales of combination products and the increased sales of single preparations that could be seen in the 1990s.

Statistics on inquiries to the Swedish Poisons Information Centre

In Figure 7 we present the development of the number of inquiries about DXP from 1995 onwards. The number of inquiries concerning DXP evidently already decreased at the end of the 1990s and a clear break in the trend took place in 2001. Between 2000 and 2002 the number of inquiries decreased by 28 per cent. The same trend as for the other results presented could also be seen here.

Figure 7 Change in number of inquiries to the Swedish Poisons Information Centre concerning poisoning with DXP from 1995 to 2002



Discussion and conclusion

The aim of this report is to evaluate any effects of the restrictions on prescribing DXP introduced at mid-year 2001. The study shows that all hypotheses presented in the introduction were verified. Sales of DXP decreased by 66 per cent from the first quarter of 1999 up to the first quarter of 2003. Moreover, the number of deceased with DXP in their blood decreased by 57 per cent from the first quarter of 2000 to the first quarter of 2003. The number of fatal cases of DXP poisoning decreased in the same period by 62 per cent. The number of discharge reports received by the Swedish Poisons Information Centre decreased by 45 per cent between 2000 and 2002, whereas the number of inquiries concerning DXP decreased by 28 per cent in the same period.

With regard to sales of DXP and the number of fatal cases of poisoning, the decrease started before the restrictions. These changes were probably due to the media attention that these risks with DXP received on several occasions in the years preceding the introduction of the restrictions. From previous experience of the effects of campaigns and media attention we have clearly learned that such effects are limited in time and fade away if the authorities do no take official action. The conclusion is therefore drawn that the decrease seen after the introduction of restrictions is probably an effect of these and not of previous media coverage.

Index of change

The question is if it is reasonable to assume that the number of cases of poisoning as a consequence of the restrictions will decrease further or if the reduction will come to a halt. In order to make an assumption, it may be of importance to examine the changes of the different variables in relation to each other. Sales of DXP, the presence of DXP in forensic material and the number of fatal cases of DXP poisoning during the years 1992 to 2002 are shown here with a common measure (index of change) in Figure 8. 1992 is the year of reference and 100 is chosen as reference value. Each year is compared to the reference and the deviation in per cent from the reference year is given as the index of change. If sales in a given year decreased by 10 per cent in comparison with 1992, the index value is 90, whereas an increase by 10 per cent equals to an index value of 110.

Figure 8 Index of change for sales of DXP, occurrence of DXP in forensic material and number of fatal cases of DXP poisoning 1992 to 2002

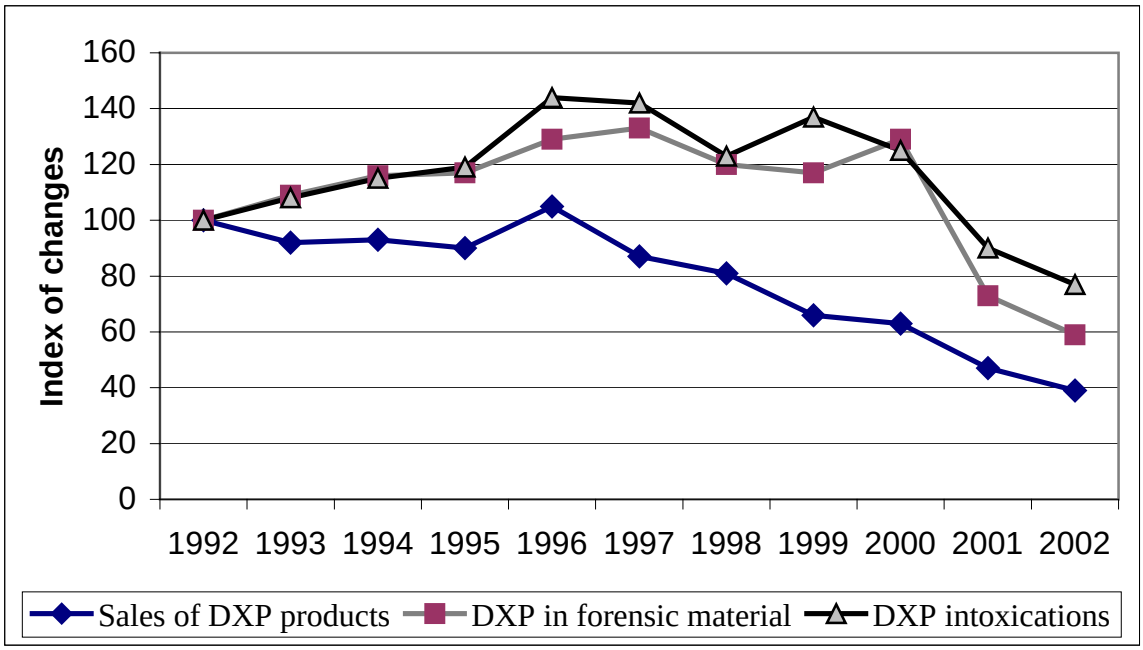


Figure 8 shows that the presence of DXP in forensic material and the number of cases of poisoning increased continuously up to the mid-1990s, by up to more than 40 per cent, in comparison with 1992. This happened in spite of a slight decrease in sales during the same period. Consequently, the increase could not be explained by a corresponding increase in sales. An explanation could be that restrictions concerning hypnotics and sedatives were introduced in 1990. This may have led to increased use of centrally acting analgesics e.g. by people who had abused the former drugs. Furthermore, the data show that in spite of the fact that sales started to decrease considerably as early as after 1996, the presence of DXP and the number of cases of poisoning remained at the same high level up to 2001 (last quarter according to Figure 2), when a substantial decrease occurred.

In total, sales of DXP decreased by 60 per cent between 1992 and 2002. The corresponding figure for the presence of DXP in forensic material is 40 per cent and for the number of fatal cases of DXP poisoning more than 20 per cent. It should be pointed out that the number of fatal cases of DXP poisoning was halved between 1996 (with a peak of 227 cases) and 2002 (122 cases). From the index of change the conclusion can be drawn that the different variables show different sensitivity to change. It may be that the economic market is more sensitive to changes and is more easily affected by 'attitudes and trends' than human habits. The publicity about the risks involved with DXP seems to have affected the market first. Only later, as a consequence of repeated publicity, reduced prescribing and the action taken by the Medical Products Agency was the consumption pattern in the population affected. In the population it seems that the 'common' user was affected first, which was shown by a decrease in the total number of individuals with DXP in their blood. Later and at a slower pace, the

consumption pattern was also affected in the groups who are at the greatest risk of dying from voluntary or involuntary DXP poisoning.

From the discussion above it would be reasonable to assume that even if sales and presence in forensic material were to remain at the same level as in 2002 a continued decrease in the number of fatal cases of DXP poisoning can be expected. However, data from the first quarter of 2003 (Figure 2) indicate a continued reduction in sales as well as the total presence of DXP in forensic material, which further strengthens the assumption that the number of cases of fatal DXP poisoning will decrease further.

In conclusion it can be observed that the decrease in the number of fatal cases of DXP poisoning shown in this study is favourable, but that this does not mean that the problem has been solved in a satisfactory way. As long as DXP is still on the market there will be new cases of poisoning. As DXP today is known to be especially dangerous, particularly in combination with alcohol, suicidal individuals will continue to choose this drug in the future. Concern over impulsive acts of suicide, the ones that are not intended to be fatal, will remain. The results of the study show that the proportion of misusers is high among those who have DXP in their blood when they die. These still constitute a considerable risk group for continued cases of DXP poisoning, both involuntary and self-inflicted on impulse.

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