TOXICOVIGILANCE COORDINATION COMMITTEE

Exposure to grade II analgesics: Updated case study compiled with the toxicovigilance and poison control centres

Report compiled at the request of *Afssaps* [French Health Products Safety Agency]

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Rapporteur

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"Medicinal products" Working group

Contributions

This work was made possible thanks to the toxicovigilance and poison control centres' recording of data originating from their day-to-day handling of requests and monitoring of the associated cases. Afssaps (Diane Hallé) provided data on the sales of the drugs that were being looked at, as well as their observed average daily dosage regimens.

Validation

This report was:

- amended by: Robert Garnier
- checked by: Laurence Lagarce, Corine Pulce, Sylvie Lerebours, Amandine Cochet and Frédéric de Bels
- validated by the "Medicinal products" working group on 19 January 2009
- validated by the operational unit on 19 January 2009

Distribution

An initial, unconsolidated version was forwarded at short notice to Afssaps on 13 November 2008.
A second unconsolidated version, incorporating adjustments to the sales figures and an update of the data (Lille), was forwarded at short notice to Afssaps on 6 January 2009.

Toxicovigilance and poison control centres (CAPTV), Afssa, Afsset, Afssaps, MSA
Sites of the toxicovigilance and poison control centres (CAPTV)

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SUMMARY

This is an update incorporating data from the toxicovigilance and poison control centres for the period from 2006-2008 into the previous study, which compared cases of exposure to dextropropoxyphene (DXP), tramadol (TRA) and codeine (COD): the sum total of all cases of exposure, symptomatic cases, cases involving convulsions, cardiovascular and respiratory complications, and death. Various adjustments were made: to the total number of cases of exposure recorded for any given substance, to the total number of cases of exposure to the drugs involved that were reported to the poison control centres and to the sales figures over the same period.

As with previous studies, although DXP was involved in the greatest number of cases, the intrinsic severity of the intoxications associated with this substance (measured in terms of the proportion of convulsions, cardiovascular or respiratory complications and deaths) was no higher than that of the intoxications associated with COD; it was indeed weaker than that of the intoxications associated with TRA.

Similarly, if one adjusts these results relative to the sales volumes by converting the latter into weeks of treatment, then whatever the indicator being looked at (total number of cases, total number of symptomatic cases, cases involving convulsions, cardiovascular or respiratory complications, or total number of cases resulting in death), DXP as a substance is not responsible for the greatest number of cases; neither is it the substance that produces complications most frequently.

These results confirm those of the previous study which this one was designed to update. Thus, according to the data from the French poison control centres, deaths pursuant to an intoxication by DXP do not appear to constitute a significant public health concern.

Moreover, France being a major consumer of DXP, any withdrawal of this active ingredient could lead to additional risks linked to having to resort to other grade II analgesics, such as TRA, when the data issued by the toxicovigilance and poison control centres regarding the latter is of greater concern.

1. Background

The safety record of dextropropoxyphene (DXP) has been challenged, mainly in Northern European countries (such as Sweden and the United Kingdom [UK]). A European assessment was carried out. For its part, Afssaps had already called upon France's toxicovigilance and poison control centres for assistance with 2 studies into the matter [1,2]. The results of the 2 studies showed that DXP did not constitute a public health concern in France [1-3]. In the absence of a European consensus on the matter, a Referral procedure is currently under way; a Rapporteur (Ireland) and a co-Rapporteur (UK) have been appointed. In order to answer their positions, Afssaps requested additional data in late October 2008 (see the instruction in Appendix 1), mainly an update to the data in the 2nd report [2] concerning the toxicity of the 3 main grade II analgesics.

2. Material and methods

A retrospective study was carried out over data covering the period from 2000 to 2008. France's *Base nationale des cas d'intoxication* (BNCI) [national database of intoxication cases] which is hosted on the jointly operated computer system of the country's toxicovigilance and poison control centres (SICAP) and the database of the toxicovigilance and poison control centre of Lille were queried comparatively for DXP, tramadol (TRA) and codeine (COD). For each of the selected substances, the following data was gathered based on the ATC codes showing in Appendix 2, for each year:

- the number of cases involving human exposure;
- the number of cases involving symptoms;
- the number of cases of death;
- the number of cases involving convulsions, as per the coding of convulsion episodes or status epilepticus;
- the number of cases involving cardiovascular complications, as per the coding of cardiac arrest, systolic arterial pressure < 80 mm Hg, cardiac arrhythmia or shock;
- the number of cases involving respiratory complications, as per the coding of apnea, bradypnea / respiratory arrest, cyanosis, acute respiratory distress syndrome (ARDS).

Each case of exposure covers a single person (= case).

In order to take into account the annual increase in the number of cases resulting from the gradual growth of the database hosted on the SICAP computer system (see Appendix 3), the results concerning DXP, COD and TRA were compared to the number of exposures to all toxic agents and to all drugs.

In order to assess the incidence of death, the number of cases of death following exposure to DXP, COD or TRA were related to the total number of cases of exposure to those same substances, and were then related to the number of deaths caused by all drugs taken together.

Moreover, in order to answer one of the questions that was raised during the Referral procedure, the deaths linked to DXP were broken down according to the circumstances of the exposure to that substance; the outcome for DXP was compared to the circumstances of all drugs taken together.

The comparisons between qualitative variables were carried out using the Pearson Chi2 test.

For each indicator, the number of cases was compared to the volume of sales (number of boxes sold) of grade II analgesics containing DXP, COD or TRA between 2000 and 2007. This information was obtained from Afssaps' database of sales of pharmaceuticals. Given that the cases that were collected by the poison control centres consisted mainly of accidental intoxications of children and suicidal behaviour, suppositories and injectable galenic forms were not taken into consideration. Only formulations designed to be taken orally and sold at community pharmacies were taken into consideration.

Another indicator was created to take into consideration the fact that:

- COD and DXP are almost always combined with paracetamol: this limits the number of treatment days per box (under French law, no box may contain more than 8 grams of paracetamol),
- as TRA is not combined with paracetamol, in most drugs containing this molecule (save for 2: Ixprim® and Zaldiar®), the number of treatment days per box is as a result far greater.

The actual content of opioid active ingredients per box was related to an average daily dosage regimen in order to obtain a number of weeks of treatment based on the information provided by the

Afssaps IMS/DOREMA database.

3. Results

France's 10 poison control centres all contributed to report.

3.1. The number of cases of exposure

Table 1 sets out the yearly numbers of cases of exposure to each of the grade II analgesics (DXP, TRA and COD), the yearly numbers of cases of exposure to all drugs and the yearly numbers of cases of exposure to all toxic agents.

Table 1. Trends in the yearly numbers of cases of exposure to DXP, COD, TRA, "all drugs" and "all toxic agents"

n	2000	2001	2002	2003	2004	2005	2006	2007	2008*	total
DXP	1,026	962	1,253	1,178	1,166	1,229	1,052	1,364	1,109	**10,339**
COD	273	279	325	295	305	344	308	442	381	**2,952**
TRA	285	280	390	400	421	500	539	752	707	**4,274**
all drugs	58,905	57,200	66,796	67,051	66,423	66,823	64,473	73,038	66,332	**587,041**
all toxic agents	144,299	141,044	165,794	165,108	166,247	166,772	163,199	181,717	161,855	**1,456,035**

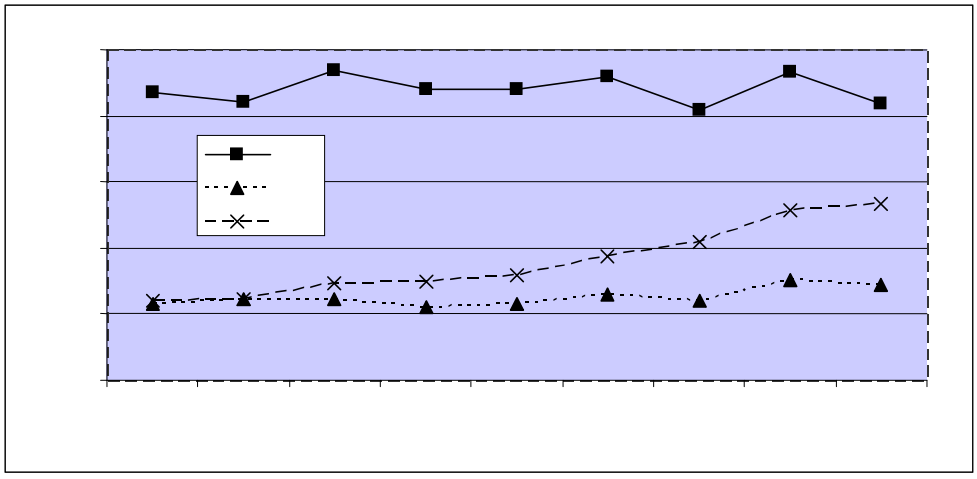
* up to 13 November inclusive.

Over the 9 year period of the data studied, 1,456,035 human cases of exposure were reported; 587,041 (43%) involved the presence of at least one drug.
DXP was present in 10,339 cases (i.e. 59% of the cases following exposure to the three grade II analgesics), COD in 2,952 cases (17%) and TRA in 4,274 cases (24%). Thus, cases of exposure to DXP were around 3.5 times more frequent than cases of exposure to COD and 2.4 times more frequent than cases of exposure to TRA.
The number of cases of exposure to DXP, COD and TRA grew in parallel to the number of cases of exposure to all toxic agents, which fits in with the gradual growth of the database hosted on the SICAP computer system (see Appendix 3).
In order to take into account this yearly increase, the results were related to the number of cases of exposure to all drugs, as shown in table 2:

Table 2. Trends in the yearly numbers of cases of exposure to DXP, COD, TRA relative to the number of cases of exposure to all drugs

Percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	1.7	1.7	1.9	1.8	1.8	1.8	1.6	1.9	1.7	**1.8**
COD	0.5	0.5	0.5	0.4	0.5	0.5	0.5	0.6	0.6	**0.5**
TRA	0.5	0.5	0.6	0.6	0.6	0.7	0.8	1.0	1.1	**0.7**

Figure 1. Trends in the yearly numbers of cases of exposure to DXP, COD, TRA relative to the number of cases of exposure all drugs



Cases of exposure to DXP and to COD appear stable over time, accounting for 1.6 to 1.9% of cases

of exposure to all drugs for DXP and 0.4 to 0.6% for COD in any given year. On the other hand, cases of exposure to TRA are seen to be increasing steadily over the years, from 0.5% in 2000 to 1.1% in 2008.

3.2. The number of deaths

Table 3 sets out the yearly number of cases of death in which DXP, COD or TRA were involved (but not necessarily responsible) versus the yearly numbers of deaths in connection with all drugs and with all toxic agents

Table 3. Trends in the yearly number of cases of death after exposure to DXP, COD, TRA, "all drugs" and "all toxic agents"

N	2000	2001	2002	2003	2004	2005	2006	2007	2008*	total
DXP	7	2	5	3	6	6	2	5	7	**43**
COD	3	0	0	1	1	0	0	2	1	**8**
TRA	0	0	0	3	4	4	4	3	3	**21**
all drugs	105	81	82	82	104	110	118	113	99	**894**
all toxic agents	233	204	197	197	256	269	238	246	205	**2,045**

* up to 13 November inclusive.

2,045 cases of death were reported by the toxicovigilance and poison control centres; 894 followed exposure to at least one drug and 72 followed exposure to one of the 3 molecules being looked at. Overall, out of these 72 cases of death, DXP was present in 43 cases (60% of the 3 grade II analgesics).
In order to take into account the yearly fluctuations, the number of cases of death following exposure to one of the 3 substances being looked at was related to the number of deaths following exposure to all drugs. The outcome is shown in table 4.

Table 4. Trends in the yearly cases of death following exposure to DXP, COD, TRA as a proportion of cases of death following exposure to all drugs

percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	6.7	2.5	6.1	3.7	5.8	5.5	1.7	4.4	7.1	**4.8**
COD	2.9	0.0	0.0	1.2	1.0	0.0	0.0	1.8	1.0	**0.9**
TRA	0.0	0.0	0.0	3.7	3.8	3.6	3.4	2.7	3.0	**2.3**

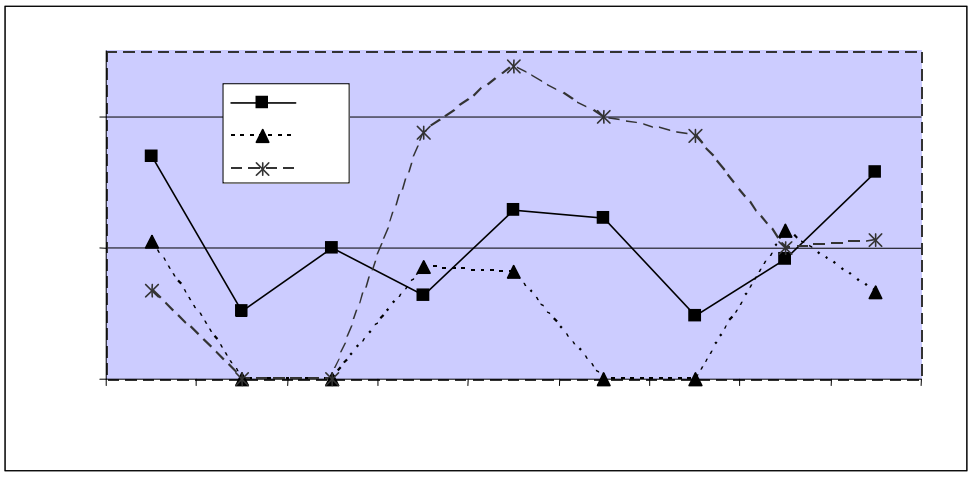
DXP was involved in 4.8% of cases of death pursuant to exposure to all drugs on average (between 1.7 and 7.1% in any given year), COD was involved in 0.9% of cases of death pursuant to exposure to all drugs on average (between 0 and 2.9% in any given year) and TRA was involved in 2.3% of cases of death pursuant to exposure to all drugs on average (between 0 and 3.8% in any given year).
By relating the number of cases of death in which one of the 3 grade II analgesics is mentioned to the respective number of cases of exposure, one can take into account the yearly fluctuations linked to the activity of the centres and obtain a death frequency as a proportion of cases of exposure to each of the grade II analgesics, as shown in table 5.

Table 5. Trends in yearly death frequency as a proportion of cases of exposure to DXP, COD, TRA

percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	0.68	0.21	0.40	0.25	0.51	0.49	0.19	0.37	0.63	**0.42**
COD	1.10	0.00	0.00	0.34	0.33	0.00	0.00	0.45	0.26	**0.27**
TRA	0.00	0.00	0.00	0.75	0.95	0.80	0.74	0.40	0.42	**0.49**

When related to the number of corresponding cases of exposure, the numbers of deaths connected with DXP, TRA and COD are of the same order of magnitude (when applying the chi2 test to the total, p=0.35). Thus the risk of death from intoxication with DXP does not seem any greater than the risks of death from the 2 other molecules.
The yearly variations witnessed with DXP and COD appear to be linked to random fluctuations. For TRA, there appears to have been an excessive number of deaths over 2003 - 2006 (a frequency of around 0.8%) compared to the other years, see figure 2.

Figure 2. Trends in the frequency of death following exposure to DXP, COD, TRA



Those deaths that were linked to exposure to DXP have been broken down according to the circumstances (table 6) based on the data from the SICAP computer system (which covers all centres except Lille, i.e. 828 cases of death and 40 in which DXP is mentioned).

Table 6. Circumstances of exposure in those cases of death involving "all drugs" and those cases of death in which DXP was involved

	Death			
Circumstance	**All drugs**		**DXP**	
	n	%	n	%
Accidental				
Routine accident	15	1.8		
Medical side-effect	117	14.1	3	7.5
Therapeutic error	29	3.5	1	2.5
Other	11	1.3		
Undetermined	8	1.0	1	2.5
Total accidental	***180***	***21.7***	***5***	***12.5***
Intentional				
Suicidal behaviour	497	60.0	32	80.0
Criminal action / malice	3	0.4		
Addiction	23	2.8		
Other	16	1.9		
Undetermined	5	0.6	1	2.5
Total intentional	***544***	***65.7***	***33***	***82.5***
Undetermined / Not specified	104	12.5	2	5.0
Total not specified	***104***	***12.6***	***2***	***5.0***
Total	**828**	**100.0**	**40**	**100.0**

If one only takes into consideration cases of exposure whose circumstances are known, deaths linked to suicidal behaviour accounted for 69% of deaths linked to exposure to all drugs, and 84% of deaths linked to exposure to DXP; this difference is significant (p = 0.04).

3.3. The number of cases of exposure involving symptoms

Table 7 shows the yearly numbers of cases of exposure involving symptoms.

DXP accounted for 53.2% of symptomatic cases involving either of the 3 grade II analgesics being looked at. In absolute terms, the number of cases involving DXP was thus nearly twice as high as the number of cases involving each the 2 other molecules. This trend is less clear-cut since 2007, with a growing number of symptomatic cases involving the presence of TRA.

Table 7. Trends in the yearly number of cases involving symptoms after exposure to DXP, COD, TRA, to all drugs and to all toxic agents

n	2000	2001	2002	2003	2004	2005	2006	2007	2008*	total
DXP	525	454	626	581	568	642	528	708	584	**5,216**
COD	144	143	201	163	164	197	169	248	222	**1,651**
TRA	188	187	266	274	288	352	387	513	484	**2,939**
all drugs	17,133	15,503	19,507	18,696	17,973	17,948	16,907	19,671	18,307	**161,645**
all toxic agents	47,690	46,007	58,321	57,533	57,855	57,223	57,023	63,963	60,089	**505,704**

* up to 13 November inclusive.

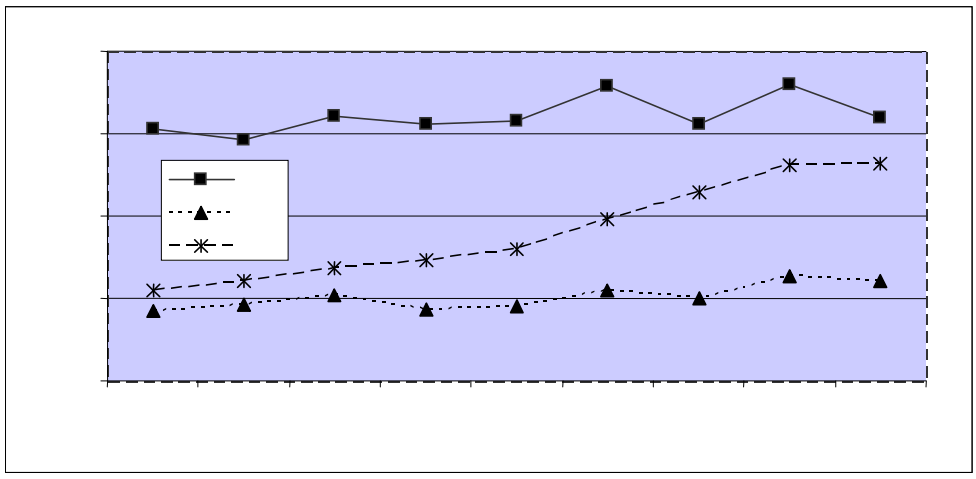
In table 8, the number of symptomatic cases involving each of the three analgesics has been related to the number of symptomatic cases involving all drugs.

Table 8. Trends in the yearly proportion of cases involving symptoms after exposure to DXP, COD, TRA out of cases involving symptoms after exposure to all drugs

percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	3.1	2.9	3.2	3.1	3.2	3.6	3.1	3.6	3.2	**3.2**
COD	0.8	0.9	1.0	0.9	0.9	1.1	1.0	1.3	1.2	**1.0**
TRA	1.1	1.2	1.4	1.5	1.6	2.0	2.3	2.6	2.6	**1.8**

Symptomatic cases involving DXP were most frequent. The frequency of symptomatic cases involving exposure to DXP was stable over time. Conversely, the frequency of symptomatic cases involving TRA has been increasing steadily since 2000 (figure 3).

Figure 3. Trends in the yearly proportion of cases involving symptoms after exposure to DXP, COD, TRA out of cases involving symptoms after exposure to all drugs



The proportion of symptomatic cases (number of symptomatic cases divided by total number of cases of exposure to any given substance) was stable over time for all 3 grade II analgesics: around 50% for DXP, between 51.3 and 61.8% for COD and around 70% for TRA (table 9). These differences are significant (Pearson Chi2 over all years taken together, for both the global test and 2 by 2 comparisons: $p < 0.001$ for all tests).

Table 9. Trends in the yearly proportion of symptomatic cases out of the total number of cases of exposure to DXP, COD, TRA

percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	51.2	47.2	50.0	49.3	48.7	52.2	50.2	51.9	52.7	**50.4**
COD	52.7	51.3	61.8	55.3	53.8	57.3	54.9	56.1	58.3	**55.9**
TRA	66.0	66.8	68.2	68.5	68.4	70.4	71.8	68.2	68.5	**68.8**

These symptoms are broken down into convulsions, cardiac complications and respiratory complications below.

3.4. The number of cases of exposure involving convulsions

Table 10 shows the yearly trends in the number of cases of exposure involving convulsions.

Table 10. Trends in the yearly number of cases involving convulsions after exposure to DXP, COD, TRA, to all drugs and to all toxic agents

n	2000	2001	2002	2003	2004	2005	2006	2007	2008*	total
DXP	5	5	4	8	2	4	3	8	8	**47**
COD	2	0	0	0	0	1	0	2	1	**6**
TRA	3	9	7	11	10	20	21	18	19	**118**
all drugs	137	145	159	181	177	173	163	167	126	**1,428**
all toxic agents	314	311	322	339	330	315	338	329	282	**2,880**

* up to 13 November inclusive.

The total number of cases of convulsions linked to exposure to either one of the 3 analgesics is 171. DXP accounted for 27.5% of the cases involving either one of the grade II analgesics; TRA accounted for 69.0% of the cases.
In absolute terms, the number of cases of convulsions involving DXP and TRA is on the rise. In order to take into account yearly variations, the number of cases involving convulsions was related to the number of cases involving all drugs, as shown in table 11.

Table 11. Trends in the yearly number of cases involving convulsions following exposure to DXP, COD, TRA as a proportion of cases of convulsions following exposure to all drugs

percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	3.6	3.4	2.5	4.4	1.1	2.3	1.8	4.8	6.3	**3.3**
COD	1.5	0.0	0.0	0.0	0.0	0.6	0.0	1.2	0.8	**0.4**
TRA	2.2	6.2	4.4	6.1	5.6	11.6	12.9	10.8	15.1	**8.3**

Cases of convulsions after exposure to TRA appeared to be overall twice as frequent as after exposure to DXP and 16 times more frequent than after exposure to COD. The incidence of cases of exposure to TRA that were followed by convulsions has been rising since 2001 (figure 4). The number of cases of convulsions involving DXP has been increasing over the past 2 years, but to a lesser extent.

Figure 4. Trends in the yearly number of cases involving convulsions following exposure to DXP, COD, TRA as a proportion of cases of convulsions following exposure to all drugs

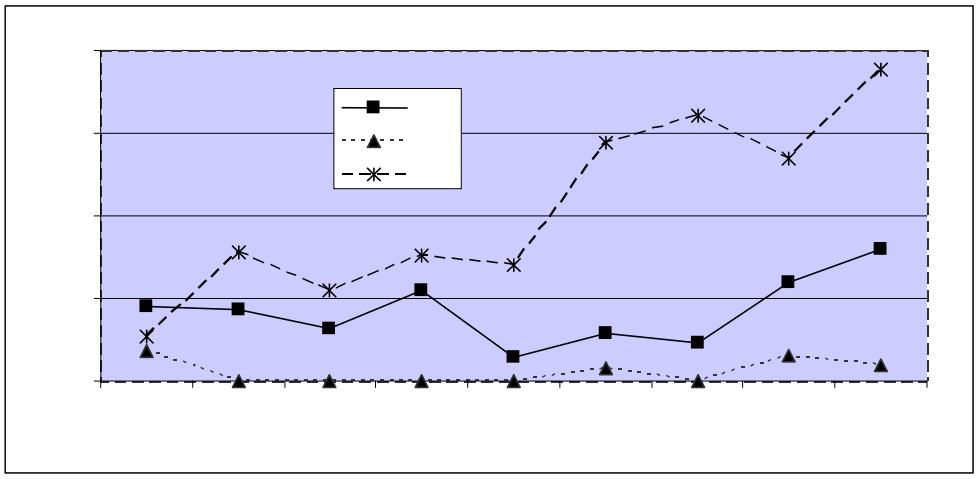


Table 12 shows the proportion of cases of exposure involving convulsions per grade II analgesic (number of cases involving convulsions related to total number of cases of exposure involving any given substance).

Table 12. Trends in the yearly proportion of cases involving convulsions as a proportion of all cases of exposure to DXP, COD, TRA

Percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	0.49	0.52	0.32	0.68	0.17	0.33	0.29	0.59	0.72	**0.45**
COD	0.73	0.00	0.00	0.00	0.00	0.29	0.00	0.45	0.26	**0.20**
TRA	1.05	3.21	1.79	2.75	2.38	4.00	3.90	2.39	2.69	**2.76**

Overall, when related to the respective numbers of cases of exposure to the drugs being looked at, cases involving convulsions following exposure to TRA appeared to be 6 times more frequent than following exposure to DXP ($p < 0.001$), and 13 times more frequent than following exposure to COD ($p < 0.001$) (Pearson Chi2, global test: $p < 0.001$).

3.5. The number of cases of exposure involving cardiovascular complications

Table 13 shows the yearly trends in the number of cases of exposure involving cardiovascular complications.

Table 13. Trends in the yearly number of cases involving cardiovascular complications following exposure to DXP, COD, TRA, "all drugs" and "all toxic agents"

n	2000	2001	2002	2003	2004	2005	2006	2007	2008*	total
DXP	10	11	19	12	22	23	20	19	25	**161**
COD	5	3	5	2	2	5	4	9	12	**47**
TRA	2	6	5	4	10	15	11	18	25	**96**
all drugs	446	386	441	466	526	569	577	661	568	**4,640**
all toxic agents	623	528	626	610	744	760	891	946	814	**6,542**

* up to 13 November inclusive.

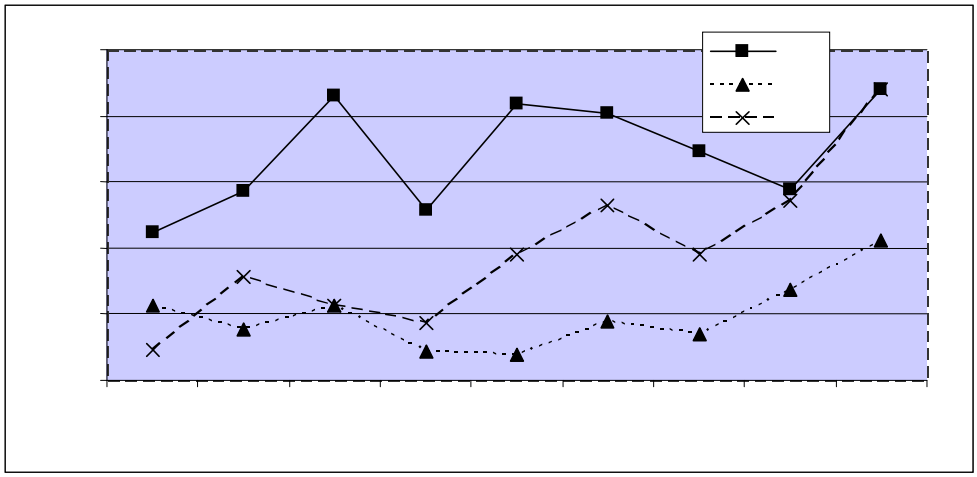
The total number of cases involving cardiovascular complications was 304, with DXP accounting for approximately half (53.0%) and TRA accounting for 31.6%. In order to take into account the apparent yearly increase in these complications, the cases were related to the number of cases of cardiovascular complications following exposure to all drugs, as shown in table 14.

Table 14. Trends in the yearly number of cases involving cardiovascular complications following exposure to DXP, COD, TRA as a proportion of cases involving cardiovascular complications following exposure to all drugs

Percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	2.2	2.8	4.3	2.6	4.2	4.0	3.5	2.9	4.4	**3.5**
COD	1.1	0.8	1.1	0.4	0.4	0.9	0.7	1.4	2.1	**1.0**
TRA	0.4	1.6	1.1	0.9	1.9	2.6	1.9	2.7	4.4	**2.1**

Cases involving cardiovascular complications after exposure to DXP appeared to be nearly twice as frequent as those arising after exposure to TRA and 3.5 times as frequent as those arising after exposure to COD. As far as DXP is concerned, the yearly variations appear to be linked to random fluctuations; as far as TRA is concerned, the yearly variations show an increase in the frequency of cardiovascular complications (figure 5).

Figure 5. Trends in the yearly number of cases involving cardiovascular complications following exposure to DXP, COD, TRA as a proportion of cases involving cardiovascular complications following exposure to all drugs



When the number of cases involving cardiovascular complications for a given substance is related to the total number of cases of exposure to that substance, cardiovascular complications appear to be significantly more frequent after exposure to TRA (overall Pearson Chi2, p = 0.02; comparison of TRA - DXP, p = 0.004; comparison of TRA - COD, p = 0.05), as shown in table 15.

Table 15. Trends in the yearly numbers of cases involving cardiovascular complications as a proportion of cases of exposure to DXP, COD, TRA

percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	1.0	1.1	1.5	1.0	1.9	1.9	1.9	1.4	2.3	**1.6**
COD	1.8	1.1	1.5	0.7	0.7	1.5	1.3	2.0	3.1	**1.6**
TRA	0.7	2.1	1.3	1.0	2.4	3.0	2.0	2.4	3.5	**2.2**

3.6. The number of cases of exposure involving respiratory complications

Table 16 shows the yearly trends in the number of cases of exposure involving respiratory complications.

Table 16. Trends in the yearly number of cases involving respiratory complications following exposure to DXP, COD, TRA, "all drugs" and "all toxic agents"

n	2000	2001	2002	2003	2004	2005	2006	2007	2008*	total
DXP	8	9	7	8	11	11	8	19	11	**92**
COD	5	7	4	3	2	11	5	7	10	**54**
TRA	10	5	11	10	18	17	13	27	22	**133**
all drugs	259	197	279	230	293	355	245	337	333	**2,528**
all toxic agents	1,395	1,289	1,654	1,659	1,909	1,840	1,962	2,177	1,984	**15,869**

* up to 13 November inclusive.

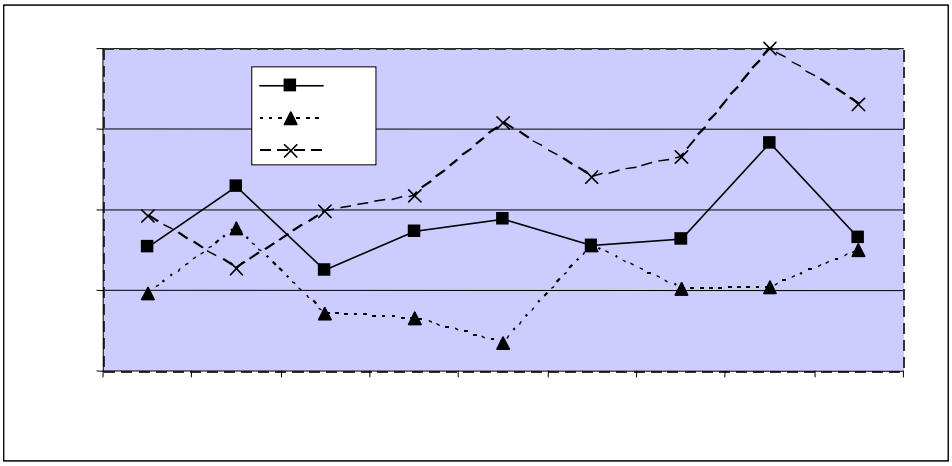
The total number of cases involving respiratory complications was 279; DXP was involving in around a third of these cases, and TRA accounted for around half (47.4%). In order to take into account yearly variations, these cases have been related to the number of cases involving all drugs, as shown in table 17.

Table 17. Trends in the yearly numbers of cases involving respiratory complications following exposure to DXP, COD and TRA as a proportion of cases involving respiratory complications following exposure to all drugs

Percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	3.1	4.6	2.5	3.5	3.8	3.1	3.3	5.6	3.3	**3.6**
COD	1.9	3.6	1.4	1.3	0.7	3.1	2.0	2.1	3.0	**2.1**
TRA	3.9	2.5	3.9	4.3	6.1	4.8	5.3	8.0	6.6	**5.3**

Cases involving respiratory complications following exposure to TRA appeared to be more frequent, and their number was seen to be increasing over the years: see figure 6.

Figure 6. Trends in the yearly numbers of cases involving respiratory complications following exposure to DXP, COD and TRA as a proportion of cases involving respiratory complications following exposure to all drugs



When the number of cases involving respiratory complications for a given substance was related to the total number of cases of exposure to that substance, respiratory complications appeared to be more frequent following exposure to TRA (Pearson Chi2, global test and 2 by 2 comparisons: for all, $p < 0.001$). They appeared to be around 4 times more frequent than following exposure to DXP and around 1.7 times more frequent than following exposure to COD, as shown in table 18:

Table 18. Trends in the yearly numbers of respiratory complications as a proportion of cases of exposure to DXP, COD, TRA

percent	2000	2001	2002	2003	2004	2005	2006	2007	2008	total
DXP	0.8	0.9	0.6	0.7	0.9	0.9	0.8	1.4	1.0	**0.9**
COD	1.8	2.5	1.2	1.0	0.7	3.2	1.6	1.6	2.6	**1.8**
TRA	3.5	1.8	2.8	2.5	4.3	3.4	2.4	3.6	3.1	**3.1**

3.7. Adjustment of the sales figures

Table 19 shows the yearly trends in the numbers of boxes of the drugs being looked at sold through community pharmacies in formulations designed to be taken orally between 2000 and 2007:

Table 19. Trends in the yearly sales volumes of DXP, COD and TRA in formulations designed to be taken orally through community pharmacies (in millions of boxes).
Source: database of sales of medicinal products, Afssaps

	2000	2001	2002	2003	2004	2005	2006	2007	total	%
DXP	77.7	80.0	85.8	87.5	86.5	93.8	91.4	84.3	**687.0**	66.4
COD	25.0	26.2	27.1	22.9	27.4	27.6	28.4	30.1	**214.7**	20.8
TRA	7.2	7.6	8.4	14.7	19.2	21.7	25.0	29.2	**132.9**	12.8

Out of some one billion boxes sold, two thirds involved drugs containing DXP; COD accounted for 20.8% and TRA accounted for 12.8%.
The conversion into weeks of treatment enables one to take into account the effect of the association of DXP with paracetamol. This is because the presence of paracetamol, owing to the limitation of 8 grams of paracetamol per box, diminishes the mass of opioid active substance per box. The average dosage regimens shown in the right hand side column of table 20 were used in order to calculate the number of weeks of treatment:

Table 20. Average daily dosage regimen of DXP, COD and TRA per quarter. Source = IMS/DOREMA database

	Average daily dosage regimen (mg)										
	2005-06	2006			2006-07	2007			2007-08	2008	Avg.
	Dec-Feb	Mar-May	Jun-Aug	Sep-Nov	Dec-Feb	Mar-May	Jun-Aug	Sep-Nov	Dec-Feb	Mar-May	
DXP	130.7	130.8	132.2	133.1	131.3	129.1	129.7	127.5	129.0	132.0	**130.5**
COD	88.5	87.4	91.2	92.9	92.6	86.9	96.5	91.1	95.0	92.2	**91.4**
TRA	222.6	222.0	228.4	229.4	225.9	228.2	220.7	205.4	218.8	227.8	**222.9**
TRA+PC	126.2	121.6	129.2	124.8	127.0	128.8	124.8	125.4	124.5	124.1	**125.6**

TRA accounted for only 12.8% of the boxes consumed, but 17% of the weeks of treatment (table 21).

Table 21. Trends in the yearly volumes of DXP, COD and TRA in formulations designed to be taken orally sold through community pharmacies (in millions of weeks of treatment)

	2000	2001	2002	2003	2004	2005	2006	2007	total	%
DXP	50.4	51.5	55.1	56.1	55.5	59.9	58.5	54.0	**441.1**	62.8
COD	16.5	17.4	17.9	14.7	18.1	18.3	18.8	20.0	**141.7**	20.2
TRA	10.7	12.4	14.5	14.7	14.7	16.0	17.6	18.5	**119.1**	17.0

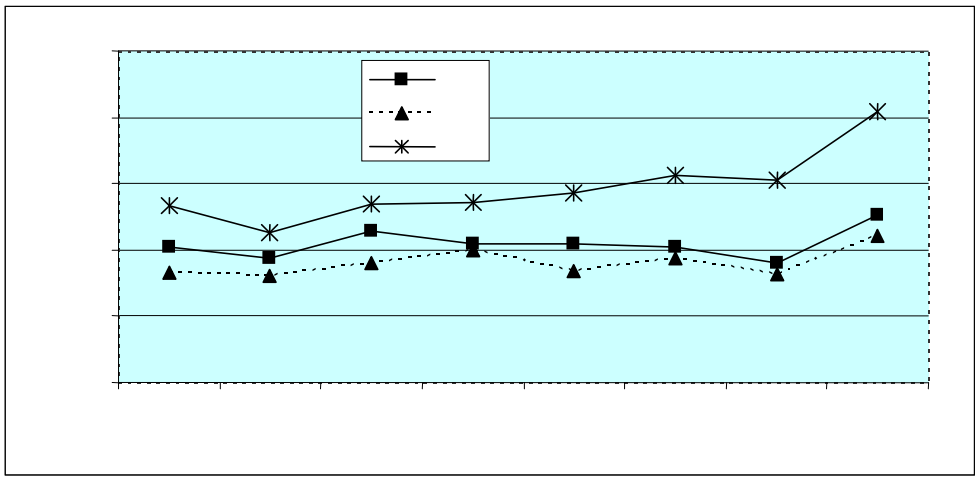
For each of the grade II analgesics, the number of cases of exposure, the number of cases involving symptoms, the number of cases of death, of convulsions, of cardiovascular or respiratory complications were related to the respective numbers of weeks of treatment in tables 22 to 27, as shown in figures 7 to 12.

Total exposure

Table 22. Trends in the yearly numbers of cases of exposure to DXP, COD or TRA in relation to the yearly sales volumes of DXP, COD, TRA (in millions of weeks of treatment)

	2000	2001	2002	2003	2004	2005	2006	2007	total
DXP	20.4	18.7	22.7	21.0	21.0	20.5	18.0	25.2	**23.4**
COD	16.6	16.1	18.1	20.0	16.9	18.8	16.4	22.1	**20.8**
TRA	26.7	22.6	26.8	27.2	28.7	31.2	30.6	40.8	**35.9**

Figure 7. Trends in the yearly numbers of cases of exposure to DXP, COD or TRA in relation to the yearly sales volumes of each drug (in millions of weeks of treatment)



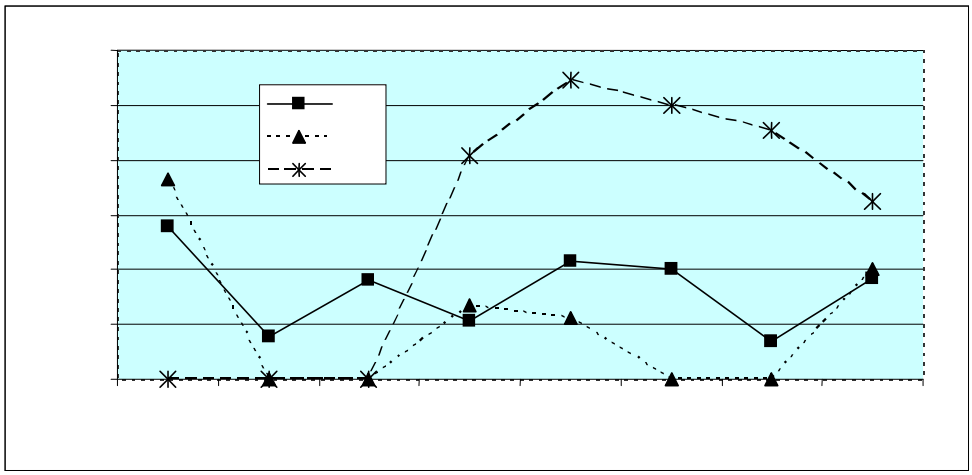
After adjusting the sales figures, exposure to DXP no longer appears most frequent (figure 1); it is exposure to TRA that is most frequent (figure 7). Moreover, the rate of exposure to TRA is growing.

Cases involving death

Table 23. Trends in the yearly number of cases of death following exposure to DXP, COD or TRA in relation to the yearly sales volume of grade II analgesics (in millions of weeks of treatment)

	2000	2001	2002	2003	2004	2005	2006	2007	Total
DXP	0.14	0.04	0.09	0.05	0.11	0.10	0.03	0.09	**0.10**
COD	0.18	0.00	0.00	0.07	0.06	0.00	0.00	0.10	**0.06**
TRA	0.00	0.00	0.00	0.20	0.27	0.25	0.23	0.16	**0.18**

Figure 8. Trends in the yearly number of cases of death following exposure to DXP, COD or TRA in relation to the yearly sales volumes of each grade II analgesic (in millions of weeks of treatment)



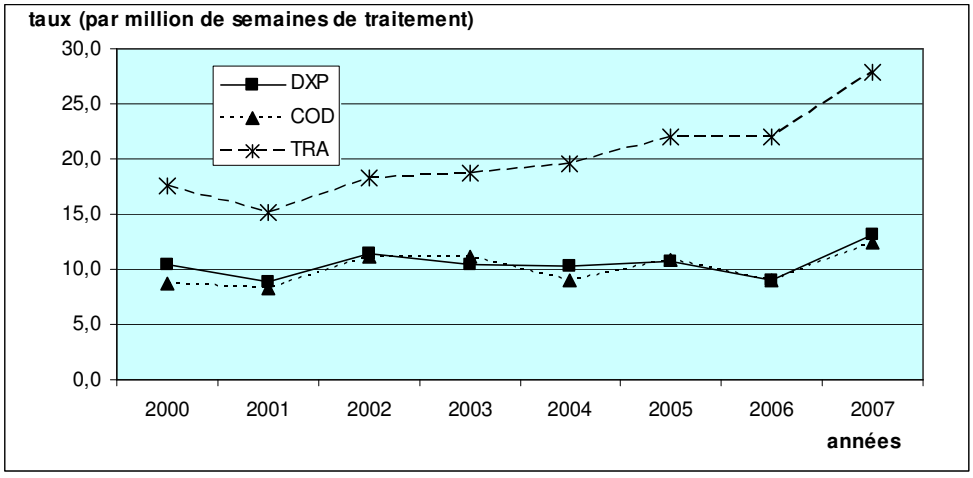
After adjusting the sales figures, cases of death appeared to be most frequent after exposure to TRA as of 2003 (figure 8), with a number of cases per million weeks of treatment that was 1.5 to 3 times higher (table 23).

Cases involving symptoms

Table 24. Trends in the yearly number of cases involving symptoms following exposure to DXP, COD or TRA relative to the yearly sales volumes of each grade II analgesic (in millions of weeks of treatment)

	2000	2001	2002	2003	2004	2005	2006	2007	total
DXP	10.4	8.8	11.4	10.4	10.2	10.7	9.0	13.1	**11.8**
COD	8.7	8.2	11.2	11.1	9.1	10.8	9.0	12.4	**11.7**
TRA	17.6	15.1	18.3	18.7	19.6	22.0	22.0	27.8	**24.7**

Figure 9. Diagram showing the trends in the yearly number of cases involving symptoms following exposure to DXP, COD or TRA relative to the yearly sales volumes of each grade II analgesic (in millions of weeks of treatment)



After adjusting the sales figures, cases involving symptoms following exposure to TRA appeared to be

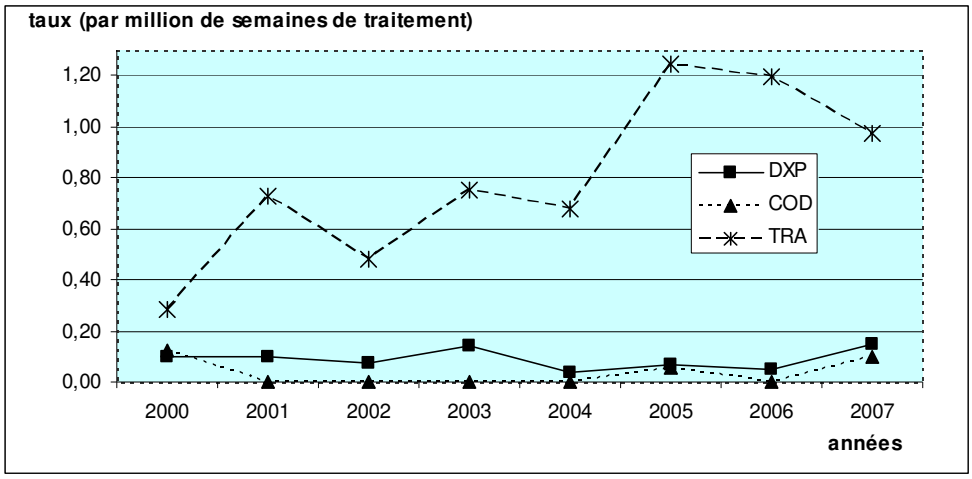
more frequent, and their number was seen to be growing steadily over the years (figure 9). Since 2004, their frequency (in millions of weeks of treatment) has been at least twice as high as for DXP or COD (table 24).

Cases involving convulsions

Table 25. Trends in the yearly number of cases involving convulsions following exposure to DXP, COD or TRA relative to the yearly sales volumes of each grade II analgesic (in millions of weeks of treatment)

	2000	2001	2002	2003	2004	2005	2006	2007	total
DXP	0.10	0.10	0.07	0.14	0.04	0.07	0.05	0.15	**0.11**
COD	0.12	0.00	0.00	0.00	0.00	0.05	0.00	0.10	**0.04**
TRA	0.28	0.73	0.48	0.75	0.68	1.25	1.19	0.98	**0.99**

Figure 10. Trends in the yearly number of cases involving convulsions following exposure to DXP, COD or TRA relative to the yearly sales volume of each grade II analgesic (in millions of weeks of treatment)



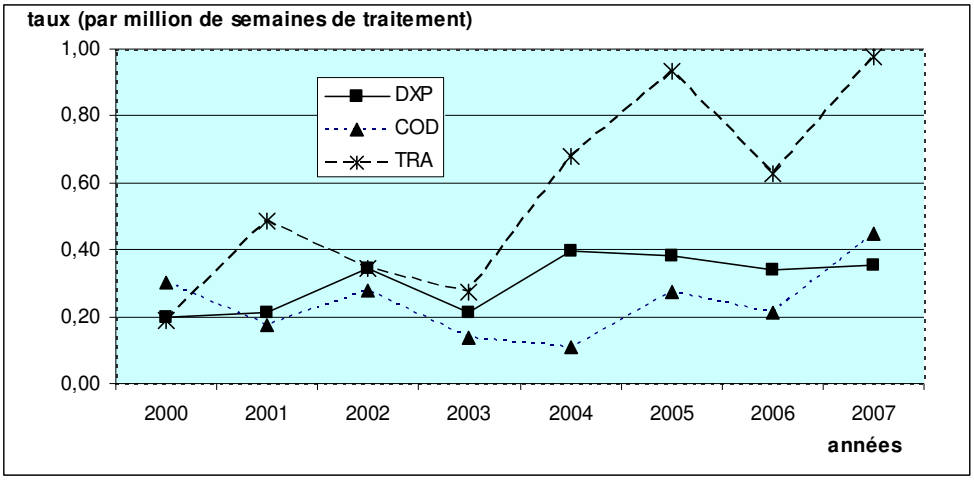
After adjusting the sales figures, cases involving convulsions appeared to be most frequent following exposure to TRA (figure 10), with a frequency per million weeks of treatment at least 5 times greater since 2001 than those witnessed following exposure to DXP or COD, whatever the year (table 25).

Cases involving cardiovascular complications

Table 26. Trends in the yearly number of cases involving cardiovascular complications following exposure to DXP, COD or TRA relative to the yearly sales volume of each grade II analgesic (in millions of weeks of treatment)

	2000	2001	2002	2003	2004	2005	2006	2007	total
DXP	0.20	0.21	0.34	0.21	0.40	0.38	0.34	0.35	**0.37**
COD	0.30	0.17	0.28	0.14	0.11	0.27	0.21	0.45	**0.33**
TRA	0.19	0.49	0.34	0.27	0.68	0.94	0.63	0.98	**0.81**

Figure 11. Trends in the yearly number of cases involving cardiovascular complications following exposure to DXP, COD or TRA relative to the yearly sales volume of each grade II analgesic (in millions of weeks of treatment)



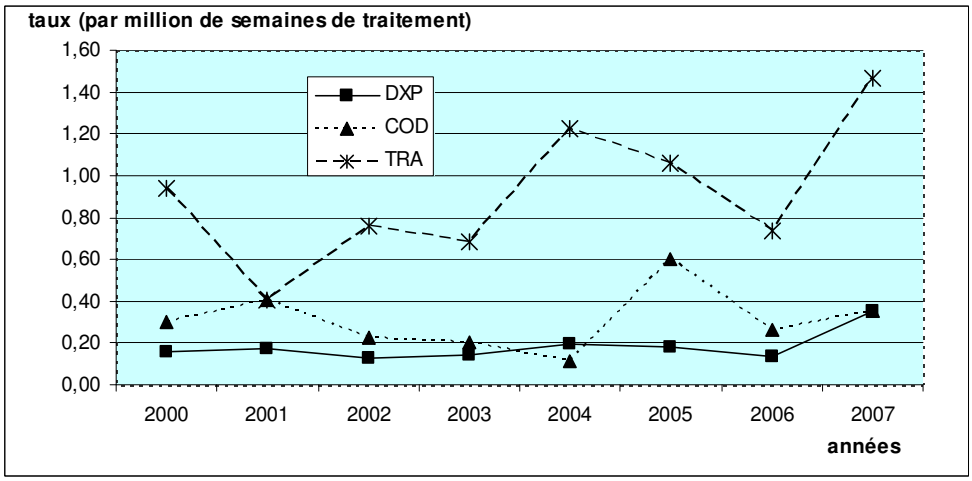
After adjusting the sales figures, it appears that since 2004, cardiovascular complications following exposure to TRA were more frequent and on the rise (figure 11).

Cases involving respiratory complications

Table 27. Trends in the yearly number of cases involving respiratory complications following exposure to DXP, COD or TRA relative to the yearly sales volume of each grade II analgesic (in millions of weeks of treatment)

	2000	2001	2002	2003	2004	2005	2006	2007	total
DXP	0.16	0.17	0.13	0.14	0.20	0.18	0.14	0.35	**0.21**
COD	0.30	0.40	0.22	0.20	0.11	0.60	0.27	0.35	**0.38**
TRA	0.94	0.40	0.76	0.68	1.23	1.06	0.74	1.46	**1.12**

Figure 12. Trends in the yearly number of cases involving respiratory complications following exposure to DXP, COD or TRA relative to the yearly sales volume of each grade II analgesic (in millions of weeks of treatment)



After adjusting the sales figures, it appears that since 2002 cases involving respiratory complications following exposure to TRA were more frequent (figure 12), with a frequency per million weeks of treatment that was at least 2 to 4 times higher than that of the other two molecules (table 27).

4. Discussion

4.1. The limitations of the study

This study was designed to update the results of a previous report that had been limited to data up to 2005. It used a method of extracting data that was different in terms of the periods covered, the way the data was handled and the contributions of the various centres. As a result, the data for previous years may differ.

In order to minimise the possible effect of variations from year to year of the number of calls to French poison control and toxicovigilance centres and of the exhaustiveness of the data, the data was related to denominators which were thought likely to vary in a similar way: exposure to “all drugs”, and exposure to “all toxic agents”. Moreover, it is most improbable that these variations might skew the outcome of the assessment of the severity of the exposure.

4.2. Reminder of the main results

The results of this study, which covered data for the period from the year 2000 to November 2008, confirm the previous results generated based on the data provided by the French toxicovigilance and poison control centres.

Compared to tramadol (TRA) and codeine (COD):

- this study, just like the previous one [2], showed that in terms of the absolute number of cases of exposure, the number of cases of exposure involving symptoms, cardiovascular complications and death following exposure to dextropropoxyphene (DXP) were higher than the numbers of cases involving the other two substances. However, the ratio involved, which was generally in the order of 2 to 3, was actually due to the greater availability of DXP. This over-representation also applies to symptomatic cases and cardiovascular complications when the numbers of cases are related to the numbers of all drugs, but it doesn’t apply to deaths;
- when, for each of the three substances, the numbers of cases involving severe symptoms (convulsions, cardiovascular or respiratory complications, death) were related to the total number of cases of exposure to the same grade II analgesic, there appeared to be no excessive risk related to exposure to DXP, whatever the severity indicator used. However, the frequency of severe cases was higher (either significantly or not) with TRA, whatever the indicator used;
- when the frequency of severe cases was adjusted in terms of the sales volumes of the substances being looked at, intoxications following exposure to DXP and to COD were seen to be of similar gravity, but much lower than following exposure to TRA, whatever the indicator used (convulsions, cardiovascular or respiratory complications, death).

The results of the prior study are thus confirmed [4,5]. The risks linked to exposure to TRA are once again highlighted by this study, as they were in the previous studies [2,4,5].

4.3. Considerations

As in the previous reports in 2005 [1] and in 2006 [2], we should point out that:

- the data comprised:
  - cases where the grade II analgesics (DXP or TRA or COD) might have been directly responsible for the alleged side-effects (symptomatic exposure, presence of convulsions, of cardiovascular or respiratory complications, or death),
  - cases where the grade II analgesics might have contributed to the effects,
  - and cases where the grade II analgesics were not responsible for the death.

  The queries of the database did not enable a case by case analysis of the causality of the grade II analgesics such as might be based on an analytic dosage and might have confirmed the involvement of DXP, TRA or COD. That is why the number of cases of death reported as part of this study most likely constitutes an overestimation of the effects of exposure to the drugs being looked at. This overestimation of effects is not a phenomenon that is specific to the grade II analgesics that were looked at; it applies to all agents; it is therefore unlikely to have skewed the outcome of the study in a significant manner;
- conversely, given that this data was drawn from the activity of the toxicovigilance and poison control centres, pre-hospital deaths are likely to have been underestimated. These deaths could only have been factored in by analysing forensic medical records. However, this underestimation of the effects

of DXP, TRA and COD applies to all toxic agents; it is thus unlikely to have skewed the outcome of the study in a significant manner;

- the data covered cases of acute exposure; intentional intoxication was involved in 80% of deaths involving exposure to DXP; the analysis was not stratified to take the particular circumstances into consideration (intentional intoxication, accidental intoxication);
- the cardiovascular and respiratory complications might be linked; similarly, it is not impossible that there might be a correlation to a certain extent between the convulsions and one or another of these two complications.
  The fact that the convulsions were most frequently associated with exposure to TRA was in keeping with what might have been expected given the high toxic potential of this substance; however, the possible presence of cases of drug abuse could not be dismissed. In this study, as in the previous report [2], the fact that respiratory complications were more frequently associated with exposure to TRA than with the other two grade II analgesics was less expected. Similarly, cardiovascular complications were more frequently associated with exposure to TRA. In spite of the membrane stabilising effect of the DXP at strong doses, the cardiovascular complications that are associated with that substance were not more frequent than with COD, in this study;
- relative to DXP, in order to explain the difference between the death rates in France on the one hand and in Scotland, England and Sweden on the other, one must take the following into consideration:
  - the French “common practice” of favouring the use of psychotropic drugs for suicide attempts;
  - the limitation of the quantity of paracetamol that can be sold in France to 8 grams per box, which *de facto* limits the quantity of DXP that can be sold per box (owing to the systematic association of DXP with paracetamol in drugs). It is common knowledge that in suicide attempts, the dosage unit (the packaging) is a limiting factor;
  - the different nature of the sources of data. The data held by the French toxicovigilance and poison control centres might have underestimated the severity of exposure to DXP (pre-hospital mortality not recorded, see above). Conversely, the data arising from autopsy results by retaining, as is the case in Sweden, a low positivity threshold (a threshold of blood concentrations of 0.8 µg/g [6] whereas the therapeutic concentrations are comprised between 0.05 and 0.75 µg/g [7], the toxic threshold is around 1 µg/L and the lethal threshold around 2 µg/L [8]) has been found to be extremely “sensitive” and tends to overestimate the implication of exposure to DXP, by being prone to confusing “the presence of DXP at the time of death” with “the responsibility of DXP for the death”.

The results of this French study concord with those of a recent assessment conducted in the United States based on data from poison control centres between 2002 and 2006, which disclosed a death frequency for exposures to DXP that was lower than that for methadone, morphine, hydromorphone and oxycodone, similar to buprenorphine, but higher than hydrocodone [9].

5. Conclusion

The results of this study confirm those of the previous study, and show that based on the data collected from the toxicovigilance and poison control centres, and compared with the two other grade II analgesics:

- DXP is linked to a greater frequency of cases of exposure (in parallel with its greater consumption, as shown by another study),
- and that the outcome of exposure to DXP is no more severe than the outcome of exposure to COD and is indeed lower than the outcome of exposure to TRA.

Thus, according to the data from the French poison control centres, deaths resulting from intoxications involving DXP do not appear to constitute a major concern.

Moreover, France being one of the major consumers of DXP, any withdrawal of this substance might lead to additional risks resulting from having to resort to TRA, when the data issued by the toxicovigilance and poison control centres regarding the latter is not the most reassuring.

6. References

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Table 2
The distribution of the substances detected in more than 50 fatal intoxications during 1992–2002 in Sweden, and the proportion with toxic concentrations

	Substance	Total	Suicides (proportion with toxic concentrations, in %)	Uncertain cases (proportion with toxic concentrations, in %)	Accidents (proportion with toxic concentrations, in %)	Cut off concentrations (μg/g)
1	Ethanol	3341	1259 (16)	1780 (43)	302 (33)	2200
2	Propoxyphene	2011	1103 (75)	760 (71)	148 (63)	0.8

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7. Appendices

Appendix 1. Instruction

RÉPUBLIQUE FRANÇAISE

afssaps
Agence française de sécurité sanitaire des produits de santé

Direction de l'Evaluation des Médicaments et des Produits Biologiques
Service de l'évaluation et de la surveillance du risque, et de l'information
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2008 – 1947

Saint-Denis, le 27 OCT. 2008

Institut de Veille Sanitaire
Département Santé Environnement
A l'attention du Secrétariat du Comité de toxicovigilance
12, rue du Val d'Osne
94415 St Maurice Cedex France

Objet : Saisine des centres antipoison et de toxicovigilance à la procédure d'arbitrage européen selon l'article 31 de la Directive 2001/83/CE, concernant l'association fixe dextropropoxyphène/ paracétamol

La Commission européenne a déclenché en novembre 2007 un arbitrage selon l'article 31 de la Directive 2001/83/CE, concernant les médicaments à usage humain contenant l'association fixe dextropropoxyphène/ paracétamol. Elle considère qu'il est de l'intérêt communautaire de renvoyer cette procédure au Comité des médicaments à usage humain (CHMP) et au secrétariat de l'Agence européenne du médicament. La procédure est en cours d'instruction. Les Etats membres rapporteurs de ce dossier sont l'Irlande et le Royaume-Uni. Le CHMP doit adopter un avis destiné à la Commission européenne au cours de sa réunion de novembre 2008.

La France est hautement concernée par ce sujet. Afin de rendre un commentaire français pour cette procédure le plus complet possible, nous sollicitons la participation des centres antipoison et de toxicovigilance (CAPTV), et plus particulièrement celle du Centre antipoison et de toxicovigilance de Grenoble (Dr Philippe SAVIUC), qui avait enquêté en 2005 sur les intoxications par le dextropropoxyphène (DXP) déclarées au réseau national des CAP, puis avait réalisé une enquête avec les autres antalgiques de palier 2 (codéine et tramadol associés ou non au paracétamol) afin de comparer les résultats à ceux observés avec le DXP.

Ainsi, l'Afssaps requiert du réseau des CAPTV :

- les données de toxicovigilance depuis 2000 pour les substances dextropropoxyphène, tramadol, et si possible codéine, seuls ou en association au paracétamol ;
- l'évaluation du dossier d'arbitrage par la participation à l'élaboration des commentaires français, sur la base des rapports des deux pays rapporteurs (date estimée de circulation : 5 novembre 2008).

Nous vous remercions de la suite favorable que vous voudrez bien donner à notre demande.

Le Chef du Département de Pharmacovigilance
au Service de l'évaluation et de la surveillance
du risque, et de l'information sur le médicament

Le Dr Carmen KREFT-JAIS 1

AFSSAPS

Drugs and Biological products Assessment Division
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2008-1947

Saint-Denis, 27 October 2008

Institut de Veille Sanitaire
Health and Environment Department
For the attention of the Secretariat of the Toxicovigilance Committee
12, rue du Val d'Osne
94415 St. Maurice Cedex France

Re: Instruction issued to the toxicovigilance and poison control centres in connection with the European Referral procedure under article 31 of Directive 2001/83/EC concerning the fixed association between dextropropoxyphene and paracetamol.

In November 2007, the European Commission launched a Referral procedure under article 31 of Directive 2001/83/EC on the Community code relating to medicinal products for human use containing a fixed association between dextropropoxyphene and paracetamol. The Commission deemed that it was in the EU's interest to refer these proceedings to the Committee for Medicinal Products for Human Use (CHMP) and to the secretariat of the European Medicines Agency. The proceedings are currently pending. The appointed Rapporteur Member States of this procedure are Ireland and the United Kingdom. The CHMP is due to adopt an opinion destined for the European Commission during its meeting in November 2008.

France is closely affected by this topic. In order to deliver a French observation for these proceedings that is as comprehensive as possible, we hereby call upon the cooperation of the toxicovigilance and poison control centres and specifically the toxicovigilance and poison control centre of Grenoble (Dr. Philippe SAVIUC), which conducted a study in 2005 on intoxications involving dextropropoxyphene (DXP) declared to the national network of poison control centres, followed by a study involving the other grade II analgesics (codeine and tramadol, whether or not combined with paracetamol) in order to compare the results with those observed with DXP.

Afssaps hereby calls upon the toxicovigilance and poison control centres:

- to yield their toxicovigilance data gathered since 2000 on dextropropoxyphene, tramadol and if possible codeine, whether used alone or in combination with paracetamol;

- to assess the merits of the Referral case by helping to draw up the French observations based on the reports drawn up by the two Rapporteur countries (estimated release date: 5 November 2008).

We thank you in advance for acceding to our request.

The Head of the Pharmacovigilance Unit of the
Drug Risk and Information Assessment and Monitoring Department
Dr. Carmen KREFT-JAÏS

Appendix 2. ATC codes selected for the querying of the database

ATC codes for DXP, COD and TRA
(source WHO: http://www.whocc.no/atcddd/)
Date: 23/10/2008

CODEINE

N02AA59	**codeine, combinations excl. psycholeptics**
N02AA79	**codeine, combinations with. psycholeptics**
N02AA	natural opium alkaloids
N02A	opioids
N02	analgesics
N	nervous system

DEXTROPROPOXYPHENE

N02AC04	**dextropropoxyphene** (chloride and nasylate)
N02AC54	**dextropropoxyphene, comb. excl. psycholeptics**
N02AC74	**dextropropoxyphene, comb. with psycholeptics**
N02AC	diphenylpropylamine derivatives
N02A	opioids
N02	analgesics
N	nervous system

TRAMADOL

N02AX02	**Tramadol**
N02AX52	**tramadol, combinations**
N02AX	other opioids
N02	analgesics
N	nervous system

Appendix 3. Periods of contribution to the information systems

National database of intoxication cases on the Sicap computer system

Toxicovigilance and poison control centres	Period during which the database was being fed
Angers	November 1999 to date
Bordeaux	September 2007 to date
Lyon	November 1999 to date
Marseille	January 2002 to date
Nancy	November 1999 to date
Paris	August 1999 to date
Rennes	January 1999 – 10/06/2008
Strasbourg	February 2007 to date
Toulouse	January 2000 to date

Lille Ciguë database

Lille	1988 to date