Using a Morphine Equivalence Metric to Quantify Opioid Consumption: Examining the Capacity to Provide Effective Treatment of Debilitating Pain at the Global, Regional, and Country Levels

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Abstract
Context: Morphine has been considered the gold standard for treating moderate to severe pain, although many new opioid products and formulations have been marketed in the last two decades and should be considered when examining opioid consumption. Understanding opioid consumption is improved by using an equianalgesic measure that controls for the strengths of all examined opioids.

Objectives: The research objective was to utilize a morphine equivalence metric to determine the extent that morphine consumption relates to the total consumption of all other study opioids.

Methods: A Morphine Equivalence (ME) metric was created for morphine and for the aggregate consumption of each study opioid (Total ME), adjusted for country population to allow for uniform equianalgesic comparisons. Graphical and statistical evaluations of morphine use and Total ME consumption trends (between 1980 and 2009) were made for the global and geographic regional levels, and for selected developed and developing countries.

Results: Global morphine consumption rose dramatically in the early 1980s but has been significantly outpaced by Total ME since 1996. As expected, the extent of morphine and Total ME consumption varied notably among regions, with the Americas, Europe, and Oceania regions accounting for the highest morphine use and Total ME in 2009. Developing and least developed countries, compared to developed countries, demonstrated lower overall Total ME consumption.

Conclusion: Generally, worldwide morphine use has not increased at the rate of Total ME, especially in recent years. Examining a country's ability to effectively manage moderate to severe pain should extend beyond morphine to account for all available potent opioids.

Key words: Opioids, Morphine, Fentanyl, Morphine Equivalence, Global Opioid Consumption, Consumption Trends, Developing Countries, UN Regions

Running Head: Morphine Equivalence and Opioid Consumption

Introduction

Pain management is a critical component of palliative care, but inadequately-treated pain remains a global public health problem and is especially prevalent in low- and middle-income countries. There are many different factors that can contribute to inadequate pain relief, including practitioners' understanding of pain and knowledge of effective treatment options, as well as peoples' willingness or ability to seek medical care. However, pain management in developing countries often is additionally hampered by the lack of available medications for treating pain that is moderate or severe (i.e., potent opioid analgesics such as hydromorphone, morphine, or oxycodone).

Global medical use of opioid analgesics was influenced significantly in 1986 by the promulgation of the World Health Organization's (WHO's) report entitled Cancer Pain Relief, and again with its republication in 1996. In these documents, the WHO conceptualized a three-step analgesic ladder as a guide for recommending various pharmacologic agents depending on the severity of the pain being treated. The WHO suggests potent opioids as first-line treatment when a patient's pain has been assessed as moderate to severe (1-2). Unfortunately, some construe the WHO analgesic ladder's "step-like" approach to mean that treatment should be based on a sequential path up the steps (i.e., initial treatment should comprise the weakest medications, regardless of pain severity). It is more widely understood, however, that the analgesic ladder has come to represent that weaker medications, such as NSAIDS or codeine, not be used initially when a patient presents with severe pain because these will likely be ineffective, and create the potential to prolong patients' pain, suffering, and diminished functioning.(3)

Despite a general increase in opioid consumption throughout the world beginning around 1986, there remains a notable disparity in level of medical use between developed and developing countries. To address this inequality, the WHO has recommended that developing countries devote appropriate resources to pain and palliative care because most people who present with cancer or AIDS are diagnosed at the late stage, when pain often is prevalent and severe.(4;5) Recently, the Commission on Narcotic Drugs,(6;7) the United Nations Economic and Social Council,(8) the World Health Assembly,(9) and the WHO(10) have called on national governments to improve treatment of pain, especially in developing countries, to ensure the medical availability of opioid analgesics for this purpose, and to recognize that providing palliative care is an urgent and humanitarian responsibility. Likewise, the International Narcotics Control Board (INCB), the independent and quasi-judicial body of the United Nations, has consistently recognized the importance of opioid medications for medical purposes.(11-14) The INCB is charged with implementing the international drug control treaties, including the Single Convention on Narcotic Drugs of 1961 (the Single Convention),(15) which obligates governments to address abuse and diversion of controlled medication while maintaining their availability for legitimate medical and scientific purposes.(14)

INCB Consumption Statistics for Opioid Analgesics

The Single Convention also establishes the obligation for national governments to annually report statistics relating to controlled medication "consumption." Within the context of the Single Convention and the INCB, "consumption" refers to the total amount of an opioid that

is distributed for medical purposes to the "retail" level in a country. "Retail" in this context refers to those institutions and programs that are licensed to dispense to patients, such as hospitals, nursing homes, pharmacies, hospices and palliative care programs).(15) Researchers historically have used these consumption statistics as a proxy for medical use and as an indication of the capacity of a country to effectively treat moderate to severe pain.(16-23) The INCB employs consumption statistics for a variety of purposes, including to monitor governments' compliance with Single Convention provisions, to determine trends in global availability of opioids and other controlled drugs, and to monitor and maintain a global balance of supply and demand of opioids for medical and scientific needs.(24) Whether it is simply to identify if a country has opioids available to treat severe pain or has had substantial changes in medication availability over time, or to be used as an outcome to determine the effect of in-country efforts to improve opioid availability, consumption statistics have useful applications to describe global and national trends and to study disparities between countries.(17) As such, opioid consumption statistics provide a unique source of data for those who study and seek to improve opioid availability.

Although an important but underutilized research tool, the consumption statistics contained in INCB reports also have several limitations that must be recognized when using them as an indicator of opioid availability. First, consumption statistics provided for the most recent year may be incomplete due to governments' reporting late, not reporting at all, or submitting inaccurate reports. Such deficiencies in amounts, however, are typically corrected in subsequent years. Second, the INCB's published reports do not provide data on quantities under a half-kilogram, and report amounts between 0.5 – 0.999 kilograms as one kilogram.(13) An ability to know the exact consumption statistics related to smaller amounts is important nevertheless, especially for countries with small populations or that have recently begun to address their medical and scientific needs. Third, the statistics for some opioids do not distinguish between distinct clinical uses. For example, it is not possible to determine from the amounts reported for fentanyl the proportion used for analgesia compared to the uses for anesthesia. Being unable to accurately determine clinical uses for this opioid results in the overestimation of its availability and application for analgesic purposes. Fourth, consumption statistics do not allow for the identification of specific product formulations or dosage forms that are available within a country. Knowing whether an opioid is available in oral, parenteral, and/or transdermal formulations could provide an indication of its potential clinical use. Finally, consumption statistics represent amounts distributed to the retail level, some of which may not actually have been dispensed to or used by patients during the same year they were reported, remaining in national stocks. As a result, medication amounts reported to the INCB do not necessarily correlate completely with the quantities used annually, and may not provide an entirely accurate clinical indicator of the quality of severe pain control in a country.(18) The data, however, are especially useful when an in-country prescription database is not readily available.

The WHO and the INCB have long recognized that pain, especially pain from cancer, is inadequately managed due to poor availability and therefore low consumption of morphine in most countries, resulting in great treatment disparities among countries.(25;26) For this reason, the WHO historically has considered a country's annual consumption of morphine as an indicator of the extent that opioids are used to treat moderate to severe cancer pain, as well as an index to evaluate improvements in pain management.(2;17;22) Another potent opioid, pethidine

(meperidine), was included in this study because it commonly is used for chronic pain relief although it is not indicated for such treatment due to the accumulation of an excitotoxic metabolite.(27) However, additional opioid analgesic medications (e.g., fentanyl, hydromorphone, and oxycodone) and product formulations (e.g., oral and transdermal) have been introduced in global and national markets over the past 20 years and should be taken into consideration when studying opioid consumption in a country, in a region, or globally. Indeed, this evolution of opioid treatment options over time suggests the need to measure the relative contributions of *all* consumed medications to gauge a country's ability to provide effective pain relief.

Although some research has attempted to use INCB data to profile countries' medical use of various medications,(16;18;21) additional studies that measure aggregate opioid use would be useful to further examine the cumulative role of individual opioids for treating pain over more than 20 years. Specifically, such research could illustrate the countries for which morphine consumption alone was either prominent or negligible compared to total opioid consumption. A conceptually-robust equivalency metric, controlling for the various strengths of each studied opioid, would provide a valuable mechanism to understand opioid consumption profiles at a global, regional, and country level. This study was designed to address the following research question: To what extent does the aggregate, equivalence, consumption of specific opioid analgesics, compared to morphine consumption alone, better represent the medical use of opioids for treating moderate to severe pain at the global and regional levels and in selected countries within those regions?

Methods

Opioid Consumption Data

This study involves a retrospective quantitative examination of 30 years of INCB consumption statistics, from 1980 to 2009, for five principal opioids that are indicated for the treatment of moderate to severe pain: fentanyl, hydromorphone, morphine, oxycodone, and pethidine. The Pain & Policy Studies Group, the WHO Collaborating Center for Pain Policy and Palliative Care, annually obtains opioid consumption data directly from the Narcotics Control and Estimates Section of the INCB Secretariat, which adds to the publically-available INCB reports by providing specific amounts for quantities less than 1 kilogram, which in 2009 represented 37% of all countries.

Morphine Equivalence (ME) Metric

Internationally-accepted and approved conversion values, developed by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway (WHOCC),(28) were then applied to the INCB data to produce a Morphine Equivalence (ME) metric for each study drug. These values have existed since the early 1970s to aid the presentation of drug utilization statistics with the aim of improving drug use. The oral formulation conversion value was applied to each drug commonly administered orally, which included all opioids except for fentanyl for which the transdermal value was used.

The conversion values have been revised over time for some medications in response to the introduction of new delivery systems, the increased use of opioid formulations with different strengths, and advances in medical and scientific knowledge that demonstrate better pain relief from around-the-clock dosing than from "as needed" dosing. To prevent the temporal variability in the conversion values, this study retrospectively applied the conversion values in effect in 2009. For example, the most recent WHOCC conversion factor of 83.33 for fentanyl, established in 2005, was utilized throughout the overall time period: the change in the conversion value for fentanyl in 2005 likely reflects the increased use of a transdermal formulation that has a different strength than previous formulations of fentanyl. Although aligning specific conversion factors with their corresponding time period for all study drugs may more accurately account for the ever-evolving medical knowledge and opioid market characteristics, this process was necessary to avoid temporal statistical variation resulting primarily from changes in conversion values, which may have occurred several years after the emergence of new information or availability of novel opioid products or formulations on the market.

Each ME statistic also was adjusted for country population. This statistical adjustment allowed for uniform global, regional, and country-level equianalgesic comparisons of the consumption of morphine with other opioid medications.(20) Milligram per person consumption data for fentanyl, hydromorphone, oxycodone, and pethidine were then aggregated into a Total ME metric, for which temporal changes could be compared against those of morphine alone.

Regional Designations and Country Selection

In addition to annual global and country level ME consumption trends for morphine and the four remaining opioids representing the aggregate Total ME consumption value, regional trends were also constructed. Geographic regions were derived from the UN Statistics Division (http://unstats.un.org/unsd/methods/m49/m49regin.htm), and a single country was selected within each geographic sub-region that represents the development status of most countries in that sub-region, using the development status categories created by the UN. See Table 1 for a complete list of UN-classified regions and sub-regions, the country selected within each sub-region, and its development status. There were two exceptions to this procedure, however:

1) Because the Southern Africa sub-region is composed equally of both developed and developing countries, Botswana was selected to represent developing countries while South Africa was chosen from the developed countries, and
2) The Southern Asia sub-region consists of the same number of developed and least developed countries, so India and Nepal served to represent the developed and least developed countries, respectively.

All countries were chosen based on (a) reporting as many of the study opioids as possible, and (b) consistent reporting of these drugs over the study period, which results in the most complete trend lines for all opioids reported by the country. It is important to note, however, that it was not possible to determine the representativeness of the selected country's opioid consumption amounts or profiles when compared to other countries within the same sub-region. For the purpose of this study, the term "country" also comprises small island developing

states (e.g., Cape Verde, Cook Islands, New Caledonia, and Sao Tome and Principe) according to UN designations.

Data Analysis

ME metrics for morphine alone, as well as for the aggregate set of the four additional study drugs delineated in the previous section, were evaluated using a two-step procedure: (a) graphical representation of logarithmically-transformed trend data, and (b) statistical analyses of differences of the log-transformed trend data utilizing a paired-samples t-test procedure.

Graphical representation of trend data. Trend graphs (between 1980 and 2009) are presented of the log-transformed statistics for morphine consumption, as well as the aggregate Total ME; a logarithmic transformation was necessary to correct the non-constant variability of the trend data. These trends offer a visual representation of the extent that morphine either diverges or converges with Total ME (which does not include morphine) over time. Each trend graph also is coupled with a graph indicating the percent change in both the morphine and Total ME values each year over the previous year, which further quantifies the degree of stability for each trend series. Percent change is calculated as follows:

$$(\exp(x) - 1.0) \times 100,$$

where x = differences of the annual log-transformed ME statistic.

Graphs are presented to characterize global consumption trends, trends for geographic regions, and trends for the selected countries within these regions.

Statistical analysis of logarithmically-transformed trend data. Paired-samples t-tests were computed using the differences of the logarithmically-transformed data trends for Total ME (excluding morphine) and morphine alone to determine the strength of the association between the two data series. Two t-tests were computed for each trend line: t_1 indicates analysis of data between 1980 and 1995, and t_2 represents from 1996 to 2009. The year 1996 was considered the beginning of a new trend phase because in this year the second edition of the WHO analgesic ladder was published and, subsequently, new opioid products were manufactured and began to be marketed internationally As a result, t-tests compare the mean difference of logs for the two phases for each of the two ME series across the 30 years of data to determine temporal differences in the extent that the combined medical use of fentanyl, hydromorphone, oxycodone, and pethidine differs from that of morphine alone. T-values that achieve statistical significance will represent trend data series that are generally not concordant. Analyses were conducted for each set of global and regional trend data examined, whenever trend data were sufficient; however, country-level comparisons were calculated only when analysis of the region to which the country belonged demonstrated statistical significance.

P-value levels to denote statistical significance were different depending on the particular analysis and number of post-hoc tests. Global and regional opioid consumption results were considered significant at the $p<.05$ level. Comparisons of the countries, representing each of the geographic sub-regions within every UN-designated region, conformed to a p-value of .01 when

there were five or fewer countries (i.e., the Americas, Europe, and Oceania regions), or $p<.005$ when there were more than five countries (i.e., the Africa and Asia regions), again only when the regional analysis was significant. In this way, all country-level comparisons within a specific region are treated as a series of post-hoc comparisons to preserve power and reduce Type I error. T-values are reported only when trend data were adequate and statistical associations were found. All paired-samples t-tests were computed using IBM SPSS Statistics version 20.0.

Results

Global Opioid Consumption

The 30-year trend ending in 2009 shows that, prior to 1986, the consumption of morphine and every opioid represented by the Total ME series, was very low and stable throughout the world (see Figure 1, following *References*). After WHO announced its three-step analgesic ladder for cancer pain relief in 1986, which encouraged use of oral morphine, morphine alone not unexpectedly began to rise to a greater extent than other opioids but generally plateaued by the mid-1990s ($t_1(14)=-2.352$, $p<.05$). Since then, however, Total ME seemed to diverge from morphine and increased at a larger rate ($t_2(13)=4.782$, $p<.0001$). With the emergence of additional opioids and dosage forms in the mid-1990s, morphine became less of a valid indicator of global opioid consumption over time. For example, in 1986 there was a 1:2 ratio between global morphine and Total ME, which decreased to 1:5 by 2009.

Opioid Consumption Among UN Regional Designations

Figure 2 (following *References*) demonstrates that each of the geographic regions had overall growth in Total ME during the 30-year study period, though to different extents. Major disparities in Total ME consumption are evident among regions. The Americas region consistently had the highest Total ME of all UN regions throughout the study time frame, while Africa most frequently evidenced the lowest consumption trend. Comparing the Total ME trends for Europe and the Americas with the trends for the Africa and Asia regions illustrates the growing disparity in ME consumption between regions comprised of primarily developed countries and those with mainly developing or least-developed countries. Interestingly, Oceania's Total ME trend has overlapped with Europe's throughout the last decade, principally resulting from its lower population compared with the other regions and the influence of Australia's and New Zealand's relatively larger opioid consumption. As with Total ME, the trends for morphine use also demonstrate notable disparities among the regions. In the last few years, morphine trends for the Americas and Oceania have been largely concordant, while Europe has begun approaching the same level of use of these two regions and showing substantial trend overlap with the Americas throughout most of the study timeframe. Conversely, the levels of morphine use in Africa and Asia were much lower and very similar during most of the study timeframe.

Figure 3 (following *References*) shows the log-transformed milligram per person Total ME and morphine trends within each of the five UN regional designations.

Africa Region

Africa, a region comprised mainly of least-developed countries, consistently reported the lowest morphine and Total ME consumption levels and even experienced a slight decrease between 2004 and 2006 (see Figure 3a, following *References*). Morphine use also tended to conform to the Total ME trend, but with larger degrees of variation. Statistical analyses did not identify notable changes in the two trend phases for either Total ME or morphine.

Americas Region

Figure 3b (following *References*) illustrates that before the early 1990s, the Total ME trend for the Americas region remained very constant, while morphine use consistently increased in the early years ($t_1(14)=-2.332$, $p<.05$). It was not until the late 1990s that there was a notable and steady increase in the Total ME trend line, especially in the last six years ($t_2(13)=2.234$, $p<.05$). Contemporaneously, morphine consumption has increased only slightly since 2000, after making notable gains early in the trend, and equaling the proportion of use that was achieved in 1992. It is not surprising that consumption in high-income developed countries (e.g., Canada and the U.S.) drives the regional trend.

Asia Region

The Total ME for the Asia region, another region with many countries that are categorized as least developed, was similar to that of Africa and represented a comparatively small proportion of the global Total ME (see Figure 3c, following *References*). Although morphine use was low but increasing during most of the early trend, it has generally plateaued since 2000, while at that time the Total ME trend constantly increased. Neither the Total ME nor morphine trend lines were associated with statistically significant changes.

Europe Region

Figure 3d (following *References*) shows that Europe, a region generally consisting of developed countries, demonstrated a higher Total ME consumption compared to morphine use from 1996 onward ($t_2(13)=4.684$, $p<.0001$). Morphine use was greater than Total ME aggregate consumption throughout most of the early trend, though non-significant, but the tremendous increase in Total ME began in the late 1990s and lasted during most of the remainder of the study period.

Oceania Region

Historically, the morphine and Total ME trend lines for the Oceania region were largely superimposed until 1990 (see Figure 3e, following *References*). At that time, morphine use increased at a larger rate, but plateaued by the late 1990s and evidenced little variability; such changes in the early trend phase were not significant, however. The Total ME trend line began to increase in 2000 and overtook morphine use by 2005 ($t_2(13)=2.317$, $p<.05$). Of all countries

represented in this region, Australia and New Zealand contributed most to the aggregate opioid amounts.

Country Comparisons

There are great disparities in the amount of morphine consumed among developed, developing, and least-developed countries; the INCB has consistently reported that a small number of developed countries consume most of the morphine in the world, while the remaining countries consume only a small proportion but contain over 80% of the world's population.(29) A question remains, however, whether such striking disparities are unique to morphine consumption, or if there are there similar disparities regarding countries' Total ME. Figures 4-8 (following *References)* show the ME trend lines for each opioid in all selected countries within each of the five UN sub-regions. Overall, in many countries, morphine was a reasonable comparator to Total ME prior to 1986. Since the mid-1980s, that single opioid has generally become a less valid indicator of the potential to provide adequate treatment of moderate to severe pain. A description of the notable characteristics for opioid consumption is provided for each country in Table 2.

Discussion

Prior to 1986, the global consumption of morphine alone did not seem a reasonable indicator of analgesic treatment, compared to Total ME, even though it was placed on the WHO's list of essential medicines in 1977.(30) Beginning with the WHO's call in the mid-1980s for more attention to relieving cancer pain,(1) morphine use began to rise and almost equaled the level of Total ME by 1995. With the marketing in the mid-1990s of new drugs and formulations to treat pain, Total ME soon emerged again as the best indication of pain treatment worldwide. In fact, global morphine use generally has plateaued for more than the last decade while the medical utilization of other opioids has continued to increase.

Given the dynamic nature of opioid consumption evidenced when using country-level data, especially in the last decade, morphine use did not keep pace with Total ME when considering the entire study timeframe. These findings seem to replicate those from recent research. For example, DeConno et al.(39) analyzed opioid purchases and expenditures from 2001 to 2003 in nine western European countries and found that morphine consumption was the lowest among the study drugs, while transdermal fentanyl use was three times higher than morphine. The authors conjectured that perhaps morphine still evokes fears of addiction, while newer drugs do not have the same associations, or that there is less of an interest in marketing morphine due to its lower profit margins.(39) It is undeniable that the selection of opioids to use for pain management has been influenced by aggressive drug marketing campaigns, resulting in large increases in the consumption of transdermal fentanyl and oxycodone compared with decreasing morphine consumption.(44;45) Conclusions from such research may call into question whether morphine continues to be considered a gold standard for pain management,(46-49) at either the global or regional levels or in most countries that were evaluated. Despite the leveling off of morphine consumption globally, however, oral morphine remains an integral analgesic for the treatment of pain.(46;47;50) Immediate-release oral morphine's low cost,

coupled with its global recognition as an essential medicine, supports its first-choice procurement in low- and middle-income countries.(51;52)

Cumulatively, this evidence has positive implications, suggesting that a variety of different opioids now characterize the overall armamentarium for treating moderate to severe pain. This is especially true for fentanyl and, in recent years, oxycodone products. Presently, practitioners in higher income countries have more medications from which to choose when prolonged pain relief is the treatment objective. Cherny et al. conducted a recent survey of the availability of opioids in 21 Eastern European and 20 Western European countries.(53) Opioid formularies in Western European countries, which are primarily developed countries, consisted of a wide range of opioids, while formularies in Eastern European countries were more limited and in some cases had severe deficiencies.(53) Similarly, a study comparing opioid cost and availability in developing and developed countries found that, in developing countries, there was a lower percentage of opioid preparations available and the proportional cost of those opioids to income was higher.(54)

The Difficulty with Considering Methadone Use

Previous use of the Total ME metric has demonstrated a substantial influence of methadone,(20) but a clear interpretation of this effect is challenging due to the pervasive dual indications for this opioid. For example, the Asia region historically has reported methadone use in amounts greater than any other examined opioid. It is likely, however, that much if not most of this medication was utilized for Methadone Maintenance Treatment (MMT), and does not necessarily represent a prevalent potential for pain relief throughout the region; methadone use was predominant since the mid-1990s in the Europe and Oceania regions as well. Indeed, sharp increases in methadone consumption in many countries, which mirror the regional increases, are associated with the introduction or availability of MMT services within countries such as Albania,(32;33) China,(34) Denmark,(16) and Malaysia.(35;36) A recent systematic review of global and regional coverage of treatment services for people who inject drugs identified MMT as the most widely-available form of substitution treatment, which has been implemented in at least 61 countries worldwide.(37) Findings also demonstrate the presence of MMT programs in nearly all countries in Western Europe, North America, and "Australasia," (p. 1021)(37) while such programs are far less common in Africa, the Middle East, and Latin America.(37;38) This information substantiates the need for future research to document the treatment indications for which methadone is being used and, importantly, to develop a systematic method to disaggregate the amounts consumed for MMT, compared to uses for pain relief, for any country with an MMT infrastructure.

Limitations

Aside from the limitations previously discussed regarding the INCB consumption statistics, certain additional limitations characterize this study. First, oral formulation conversion factors were used when calculating the ME for every opioid except fentanyl, due to the inability to identify drug formulations from the INCB data. Such a method does not accurately reflect the specific variety of formulations and potencies in which the medications are available in each country and will therefore misrepresent the total amounts to an unknown degree. Second,

despite Total ME opioid consumption being a more comprehensive metric than Morphine alone, the medications used to define these metrics still may not sufficiently represent the potential for effective moderate to severe pain management in a country. Some countries use alternative opioids such as oxymorphone, hydrocodone, or levorphanol for the relief of pain; however, these were not included in the Total ME. There surely are additional historical, social, cultural, or economic factors that impact the availability and clinical use of opioids for pain care in individual countries. For example, such issues as the international variation in the growth of opioid use, as well as the differences among countries in demography, disease rates and severity of illness, and the accessibility of other pain-relieving modalities and viable treatment venues, could also be considered in future research. Third, as stated previously, the countries selected within each UN region do not necessarily represent the opioid use patterns for the remaining countries. An effort was made to choose countries according to minimal missing data and regional development status, but there was no attempt to compare the opioid consumption profiles in each country. Finally, despite these country-selection efforts, in some cases it was unavoidable to illustrate countries with incomplete consumption trend lines. Perhaps not surprisingly, least-developed countries, such as many represented in the Africa and Asia regions, demonstrated a more prevalent occurrence of missing annual data. This feature also was characteristic of the small island developing countries in the Oceania region. It is unknown whether these missing data means either that the country governments did not submit the forms documenting consumption statistics or that there was no medication use to report for that year. Further efforts are needed to determine the implications of missing data, as a different intervention is required if this occurrence represents incomplete data reporting rather than a lack of sustained availability of these medications.

Conclusions

The global per person consumption of morphine has remained relatively stable in the last decade, especially when compared to the Total ME trend. This consumption profile also generally was found at the regional and country levels, but tended to be characteristic of development status – with developing and least-developed countries demonstrating comparatively lower use of fewer medications. As a result of changes in consumption patterns, morphine no longer solely symbolizes a country's ability to effectively manage moderate to severe pain, as expressed by the increase in the Total ME metric used in this study. For reasons of cost and effectiveness, in addition to other access issues, however, morphine would still be considered the first choice opioid therapy option for many countries.

This study represents the first graphical and statistical analysis of consumption trends characterizing a broad array of both developed and developing countries, for which medication amounts were reported as ME values. Use of a Total ME metric, also controlled for country population, offers a more unambiguous indicator of the extent that a country has the pharmaceutical capacity to provide effective treatment of debilitating pain. As we have seen, even when accounting for the consumption of many opioids available within countries, there is a continuing global disparity in the use of these medications to treat moderate to severe pain, with the highest consumption occurring in high-income countries that represent a small proportion of global population. To help address this disparity, the Total ME is a metric that can be used, on a country level, to identify and measure the individual drugs that contribute to the Total ME value, thereby serving as a potential mechanism for targeting interventions to enhance access to specific

opioids according to the needs and resources of a country. It is hoped that the ME conversions used in this research, as well as the Total ME metric, will stimulate the further analysis of longitudinal medical use trends for other countries to identify and offer recommendations for opioid availability issues.

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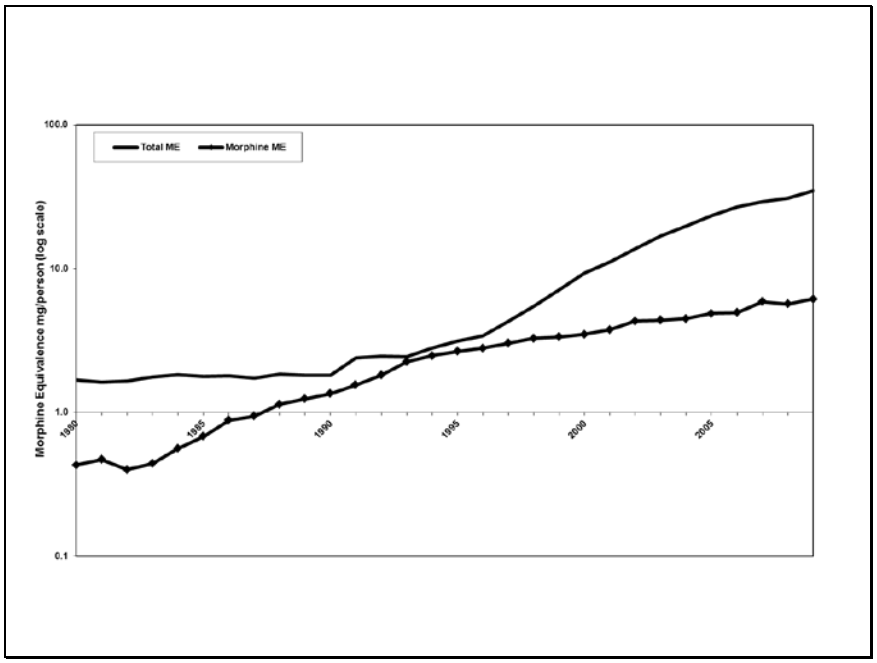
Table 1: UN Geographic Regional Designations for Selected Countries			
Regions	**Sub-Regions**	**Country**	**Development Status**
Africa	Eastern Africa	Ethiopia	Least developed country
	Middle Africa	Sao Tome & Principe	Least developed country (also classified as a Small island developing country)
	Northern Africa	Tunisia	Developed country
	Southern Africa	Botswana South Africa	Developing country Developed country
	Western Africa	Mauritius	Least developed country
Americas	Caribbean	Cuba	Small island developing country
	Central America	Nicaragua	Developed country
	South America	Ecuador	Developed country
	Northern America	Canada	Developed country
Asia	Central Asia	Uzbekistan	Developing country
	Eastern Asia	China	Developed country
	Southern Asia	India Nepal	Developed country Least developed country
	South-Eastern Asia	Malaysia	Developed country
	Western Asia	Lebanon	Developed country
Europe	Eastern Europe	Poland	Developed country
	Northern Europe	Denmark	Developed country
	Southern Europe	Albania	Developed country
	Western Europe	Germany	Developed country
Oceania	Australia and New Zealand	Australia	Developed country
	Melanesia	New Caledonia	Small island developing country
	Micronesia	Kiribati	Small island developing country
	Polynesia	Cook Islands	Small island developing country

Table 2: Description of Country Trends for Study Opioids (log scale)		
Regions	**Country**	**Trend Descriptions**
Africa	Ethiopia	The Total ME trend was generally higher than morphine alone during the study period. Morphine was used in the early 1980s throughout the early 1990s, and sporadically thereafter. In 2008, morphine use notably increased, even overtaking Total ME, but it is too early to determine if elevated morphine use will continue as a trend.
	Sao Tome & Principe	Morphine use was evident until the mid-1990s, whereas Total ME has been constantly present (although at various rates) over the study timeframe.
	Tunisia	Since the early 1990s there were periodic increases in both the morphine and Total ME trends. Morphine use tended to rise until 2009, but Total ME became more stable by 2005 and subsequently.
	Botswana	Morphine and Total ME trends were highly discordant during most of the 1980s. Since the early 1990s when morphine use began to increase, there was a general concordance between morphine use and Total ME, which also includes large trend variability.
	South Africa	Morphine use generally dominated over the Total ME metric during the entire study timeframe. Although, Total ME demonstrated a prolonged and relatively uniform presence, morphine continues to be the most-used study opioid.
	Mauritius	Except in a few years, there was a large discordance between morphine use and Total ME. In recent years, however, Morphine consumption has begun to rise while Total ME has decreased.
Americas	Cuba	Total ME was most prominent throughout the 1980s and in the late 1990s. However, morphine consumption has grown since the early 1990s but became more stable after 2000.
	Nicaragua	The study drugs were relatively unavailable during the 1980s. Aside from a one-year surge in 1992, Total ME principally remained unchanged since the early 1990s. Morphine use has increased since the early 1990s and has almost equaled Total ME in the last few years.
	Ecuador	The Total ME trend has shown a historical discordance with morphine. In the last few years, however, although morphine availability has been sporadic, its trend has continued to rise to a higher degree than Total ME.
	Canada	Although morphine consumption grew at a faster rate than Total ME, with largely overlapping trends from the late 1980s to the mid-1990s, morphine use has not changed drastically since the late 1990s. The Total ME trend has become increasingly divergent from that of morphine in the last decade ($t_2(13)=3.673$, $p<.003$).
Asia	Uzbekistan	Total ME has not kept pace with morphine use since data became available in the late 1990s. For most of this timeframe, morphine was the most highly-consumed medication; however, its overall per person use was minimal compared to most other developed, or even developing, countries.
	China	There has been increasing convergence between morphine consumption and the Total ME trend throughout the study period. Influence on the Total ME trend from the growing use of other opioids has been apparent since the early 2000s.
	India	The Total ME trend has maintained a relatively constant level over the study period. Although morphine use was higher in the mid- to late-1980s, it declined and was generally surpassed by Total ME through most of the remainder of the study phase. Morphine use was again documented in 2007, 2008, and 2009, achieving pre-1990 levels, but it is difficult to determine whether the medical use of this drug will continue.

	Nepal	It was not until the mid-1990s that opioids became consistently available, but was limited primarily to morphine. Predominance of the Total ME trend changed notably in 2005 when morphine consumption surpassed that of Total ME.
	Malaysia	Both the Total ME and morphine trends grew over the 30-year timeframe, with morphine use increasing at a greater rate in the early phase. Except for a few years in the late 1990s, morphine consumption has been lower than Total ME.
	Lebanon	It was not until the mid-1980s that morphine has been consistently available. Total ME was higher than morphine use throughout the study period.
Europe	Poland	It was not until the mid-1990s that Total ME and morphine use converged. The morphine trend tended to stabilize subsequent to the mid-1990s, but the Total ME trend continued to rise substantially thereafter, though not long enough to achieve statistical significance ($t_2(13)=2.255$, $p<.042$).
	Denmark	Since the mid-1980s, morphine use clearly outpaced the Total ME trend ($t_1(14)=3.412$, $p<.004$). That profile changed by the late 1990s, with morphine use falling below that of Total ME. The consumption of morphine has continued to decline somewhat, while the Total ME trend has risen to a greater extent ($t_2(13)=4.640$, $p<.0001$).
	Albania	Total ME was distinct from morphine use in the 1980s, but the two trends frequently overlapped during most of the remaining study period. Since the mid-1990s, morphine consumption has been as prominent at times as the Total ME trend, but has demonstrated greater variability.
	Germany	Although morphine use increased at a faster rate than Total ME, and was even greater than the Total ME trend from the early- to late-1990s, morphine use has not changed drastically since the late 1990s. The Total ME trend became increasingly divergent from that of morphine in the last decade ($t_2(13)=4.151$, $p<.001$).
Oceania	Australia	During the first 10 years of this study period, there was a relative clustering of the morphine and Total ME trends. This changed in the early 1990s, when the consumption of morphine increased over the next decade. Total ME began rising by the late 1990s and continued throughout the remainder of the study timeframe, but not enough to achieve statistical significance ($t_2(13)=2.111$, $p<.055$).
	New Caledonia	In the earlier part of the study period, morphine use grew more rapidly than Total ME, eventually overtaking Total ME throughout most of the 1990s. More recently, Total ME has surpassed the consumption level of morphine.
	Kiribati	The Total ME and morphine trends represent the most inconsistent reporting of consumption statistics from any country highlighted in this study, which actually reflects the erratic use of opioids in all Micronesian countries. Cumulative consumption of all study medications in recent years is at its lowest level since the mid-1990s.
	Cook Islands	Morphine consumption statistics have been reported rather consistently since 1985 and, while demonstrating much variability, has tended to increase in the last 15 years. During that same time, the Total ME trend was characterized as more stable, which allowed for an increasing convergence with morphine later in the trend series.

Figure 1. Log Scale of Global Consumption Trends for Morphine and Total Morphine Equivalence (mg/person)



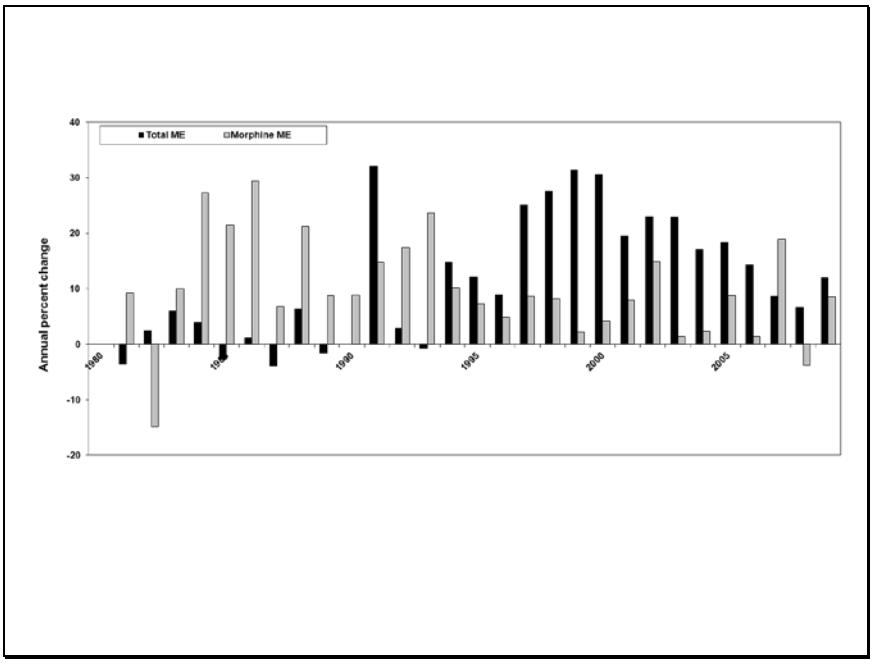


Figure 2. Log Scale of UN Regional Consumption Trends for Morphine and Total Morphine Equivalence (mg/person)

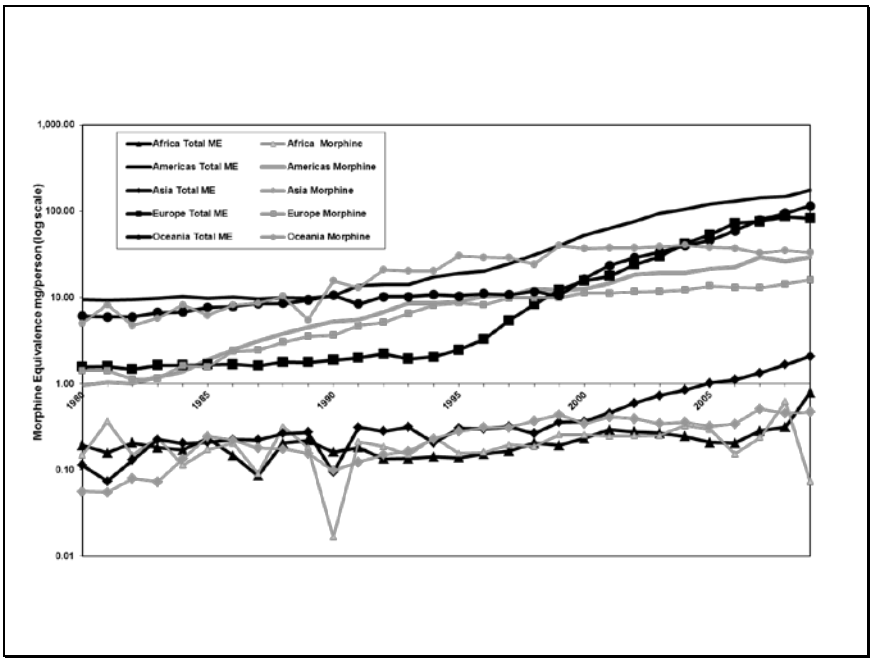
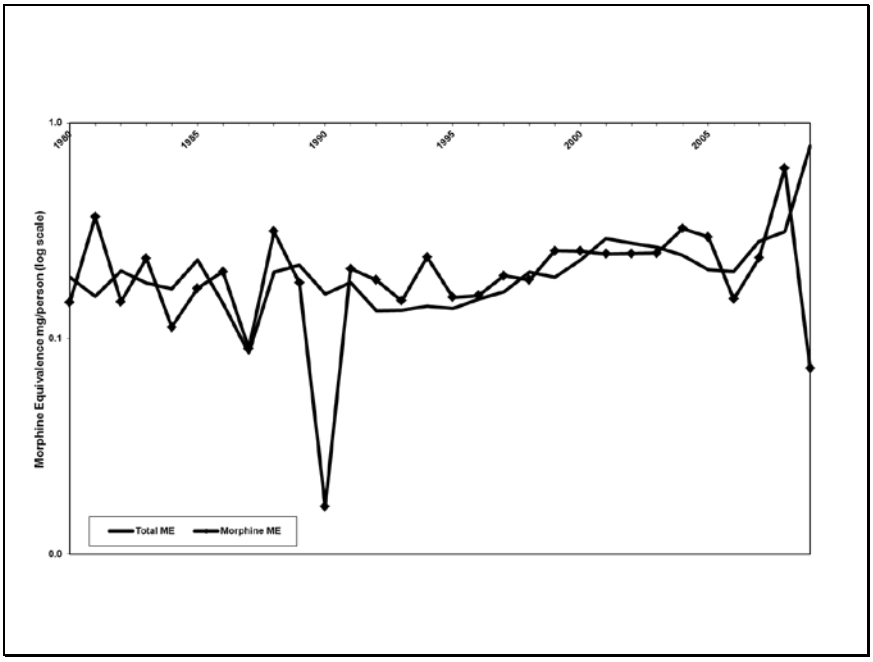


Figure 3a. (Africa) Log Scale of Consumption Trends per UN Region for Morphine and Total Morphine Equivalence (mg/person)



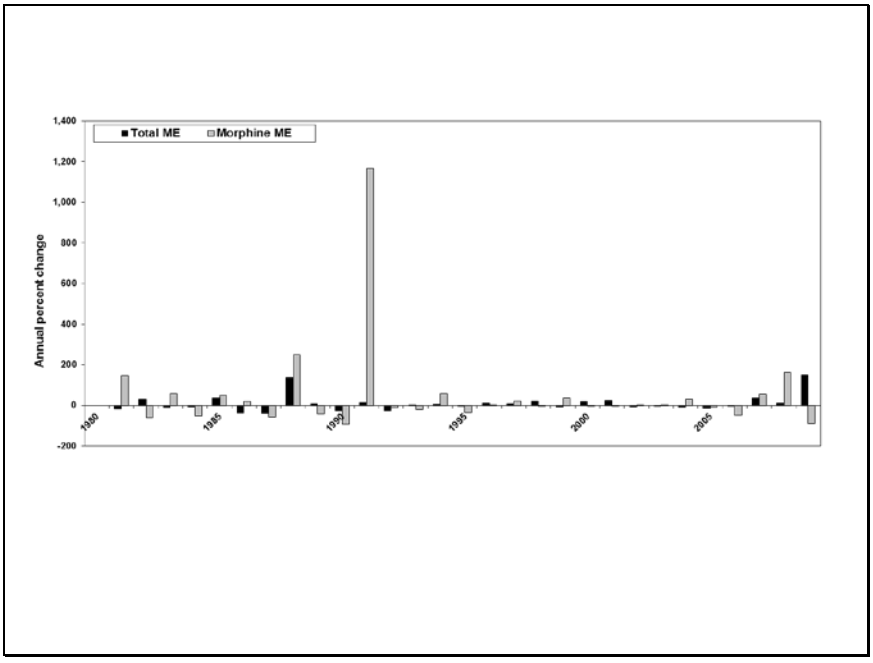
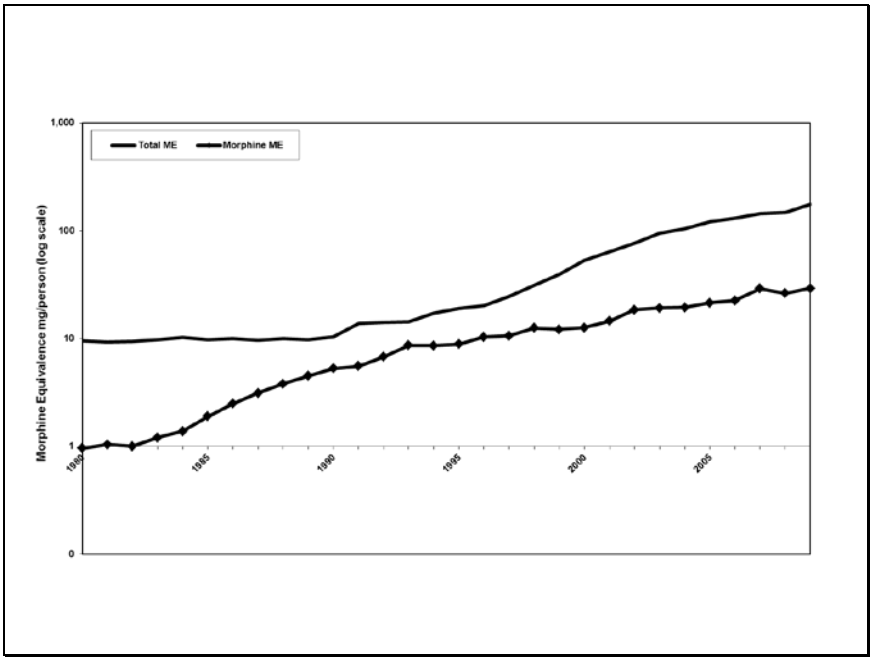


Figure 3b. (Americas) Log Scale of Consumption Trends per UN Region for Morphine and Total Morphine Equivalence (mg/person)



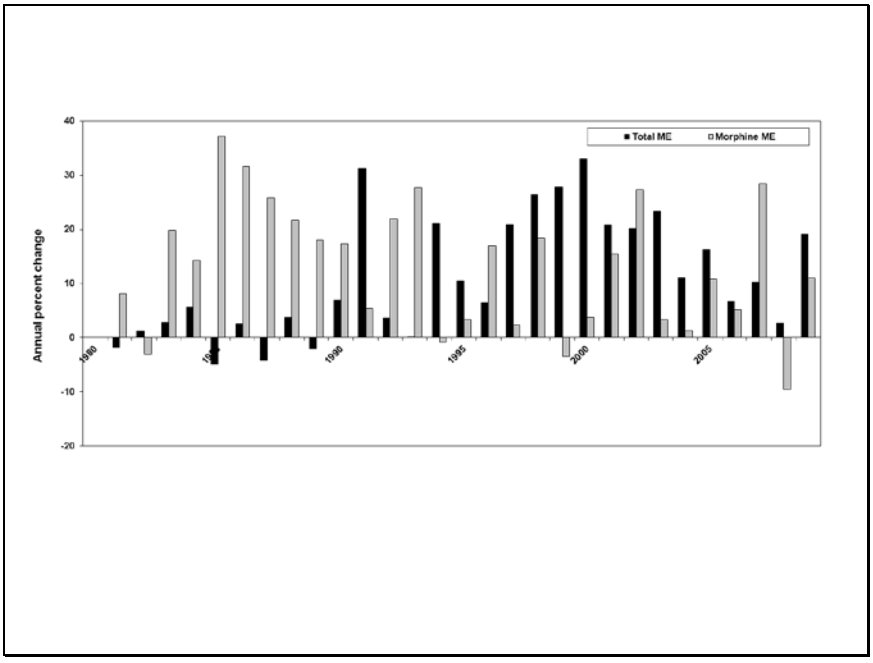
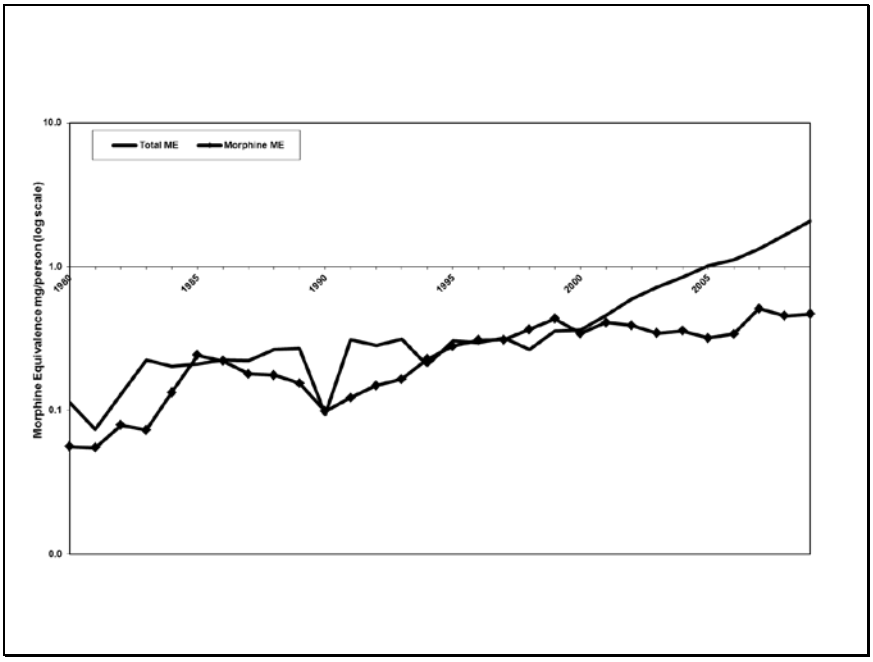


Figure 3c. (Asia) Log Scale of Consumption Trends per UN Region for Morphine and Total Morphine Equivalence (mg/person)



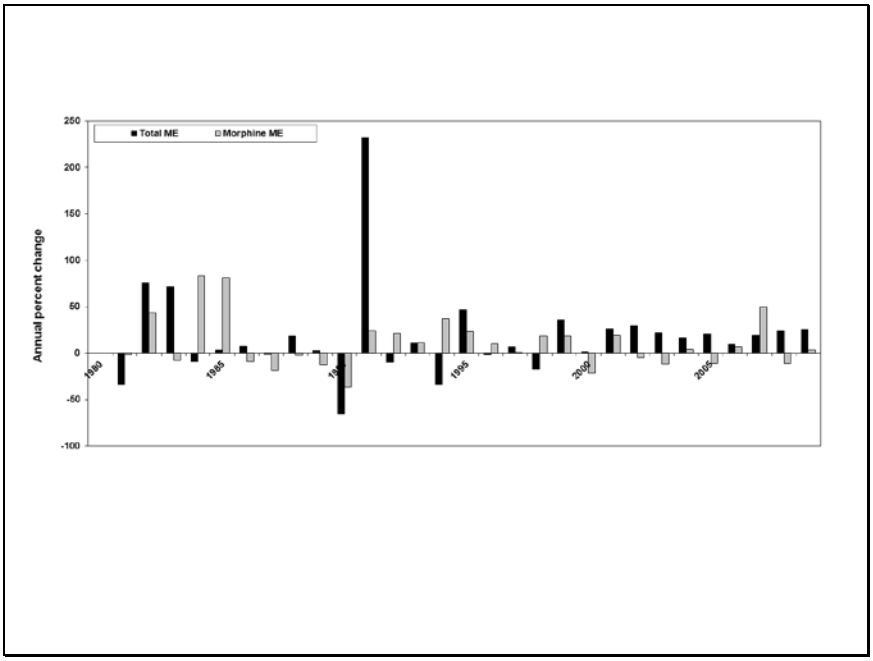
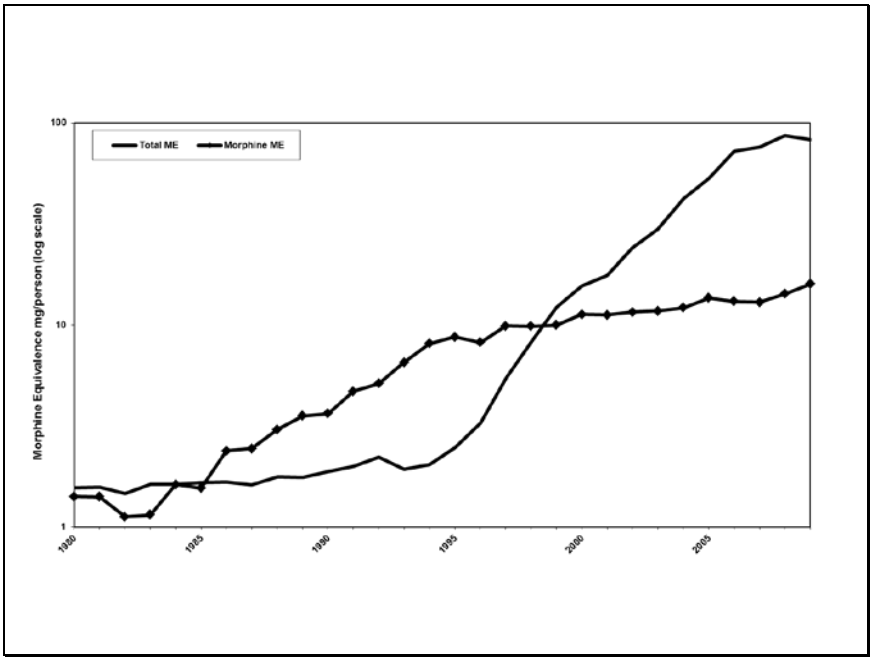


Figure 3d. (Europe) Log Scale of Consumption Trends per UN Region for Morphine and Total Morphine Equivalence (mg/person)



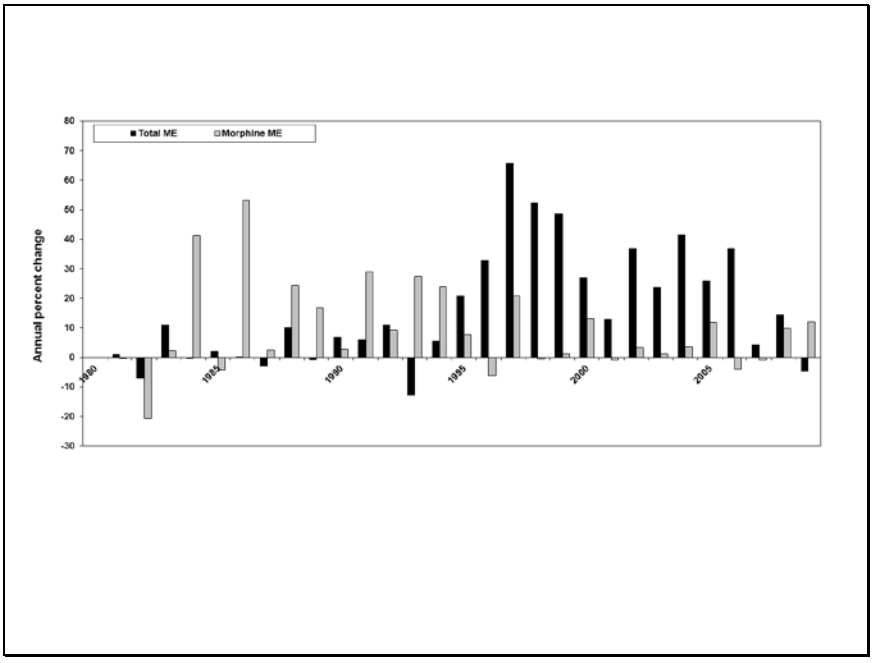
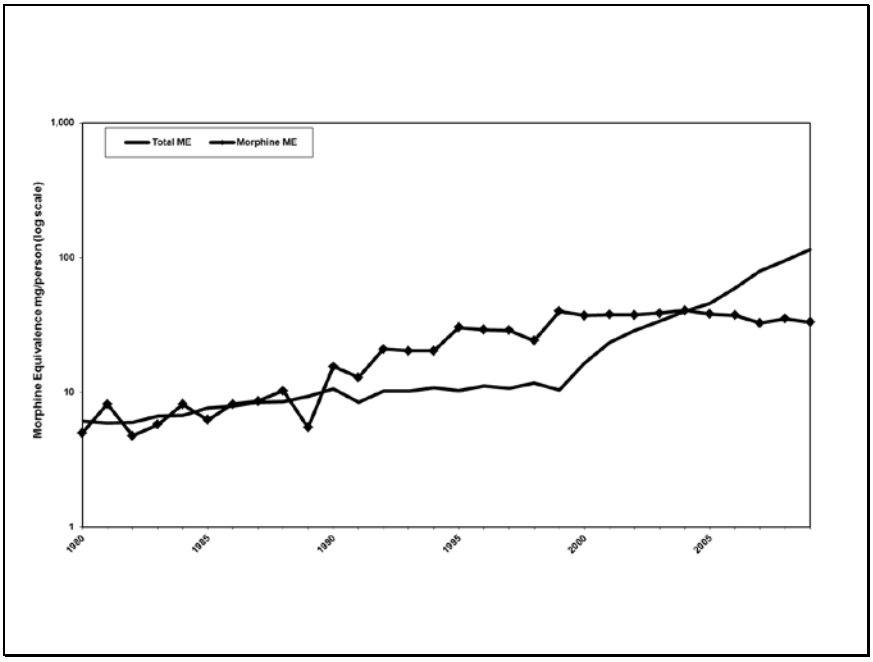


Figure 3e. (Oceania) Log Scale of Consumption Trends per UN Region for Morphine and Total Morphine Equivalence (mg/person)



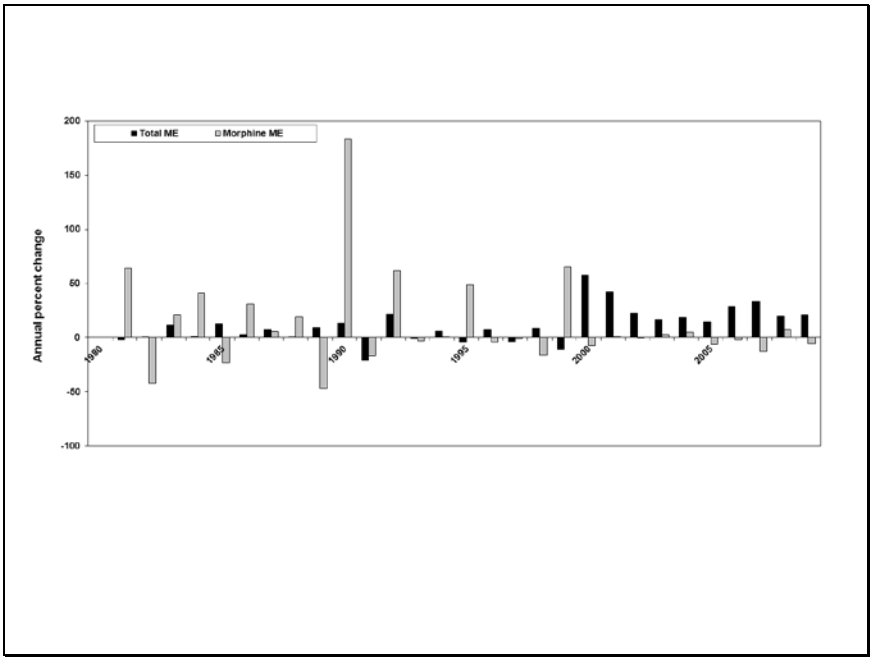
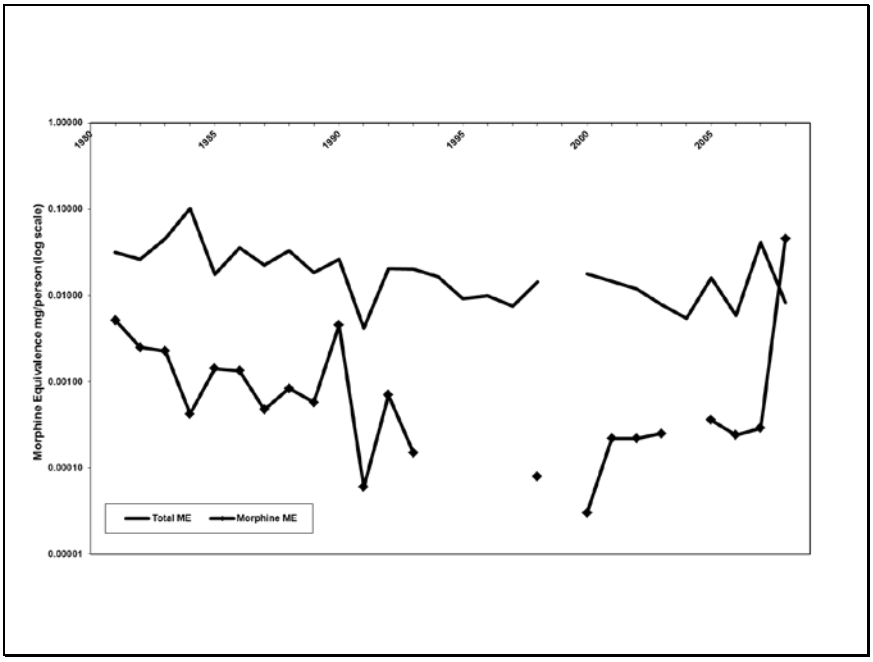


Figure 4a. (Ethiopia) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Africa Region



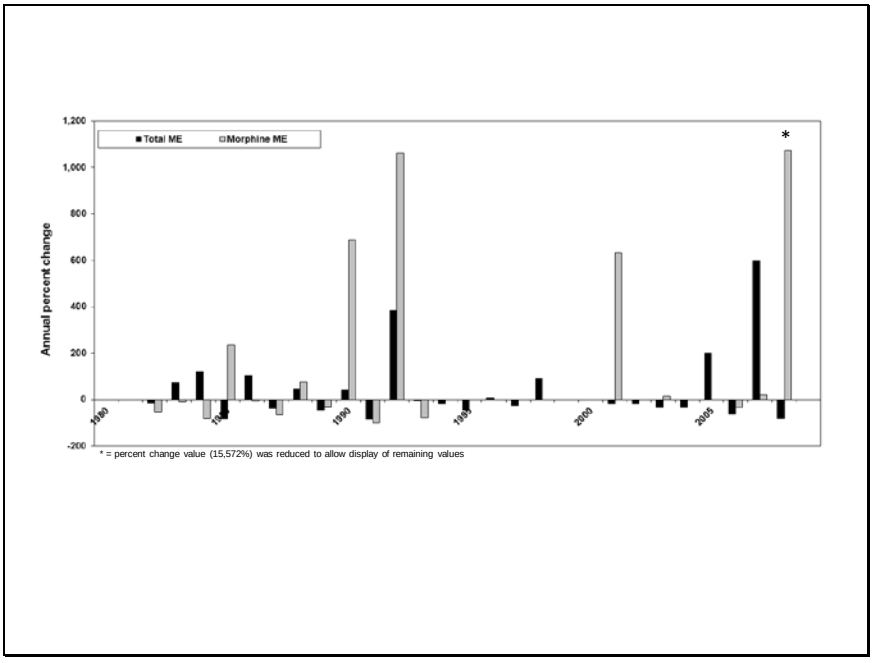
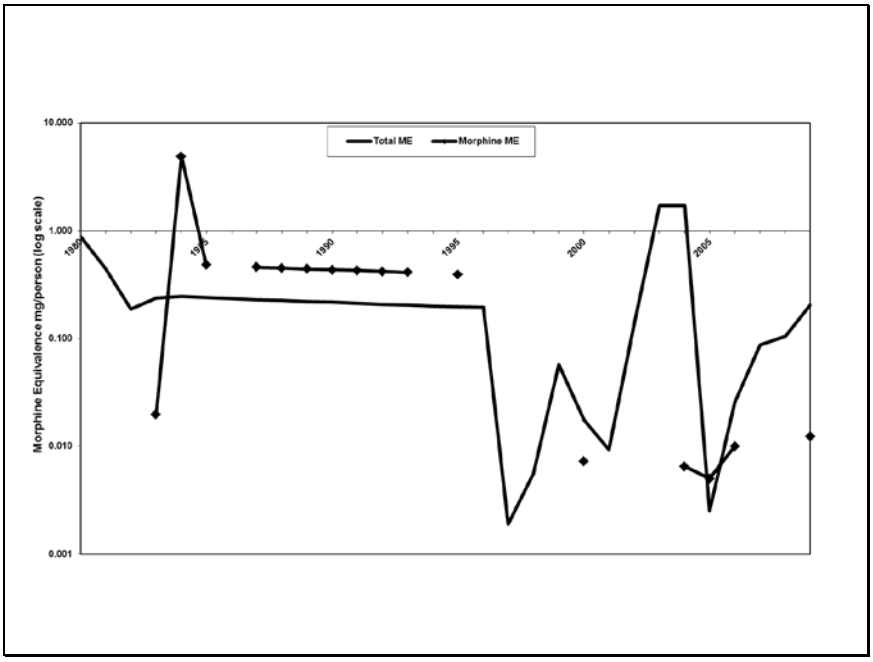


Figure 4b. (Sao Tome & Principe) Log Scale of Consumption trends for Morphine and Total Morphine Equivalence (mg/person), in the Africa Region



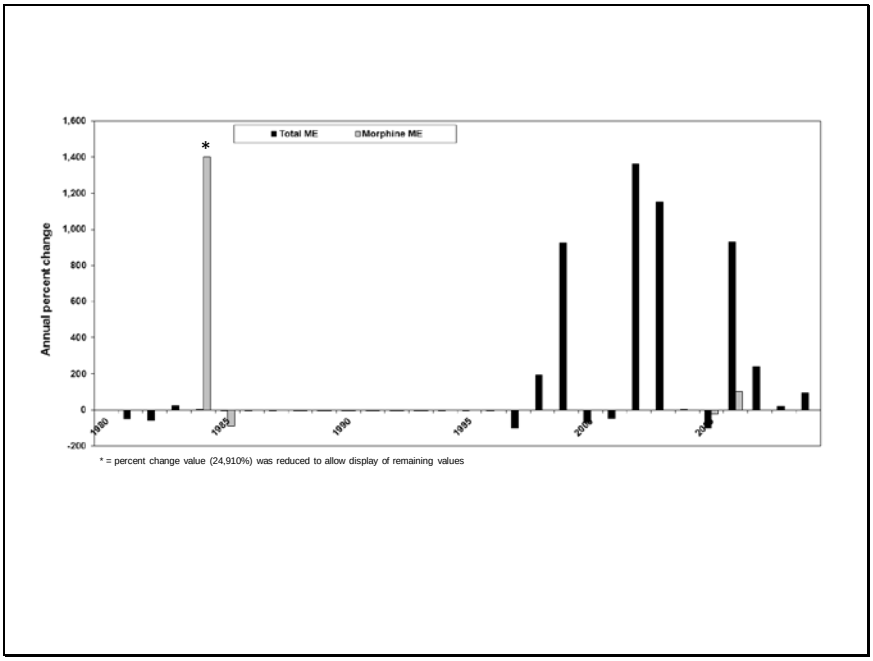
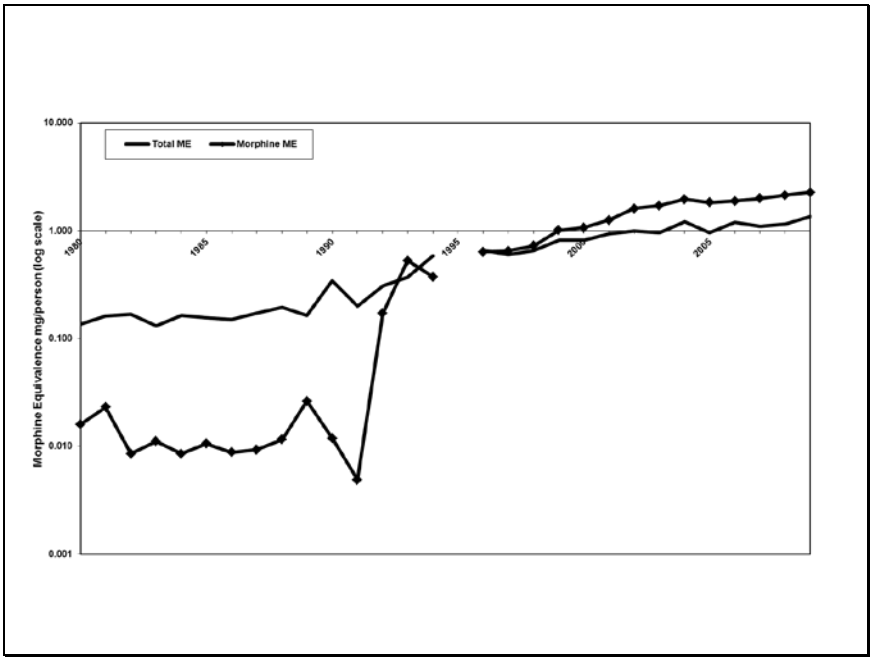


Figure 4c. (Tunisia) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Africa Region



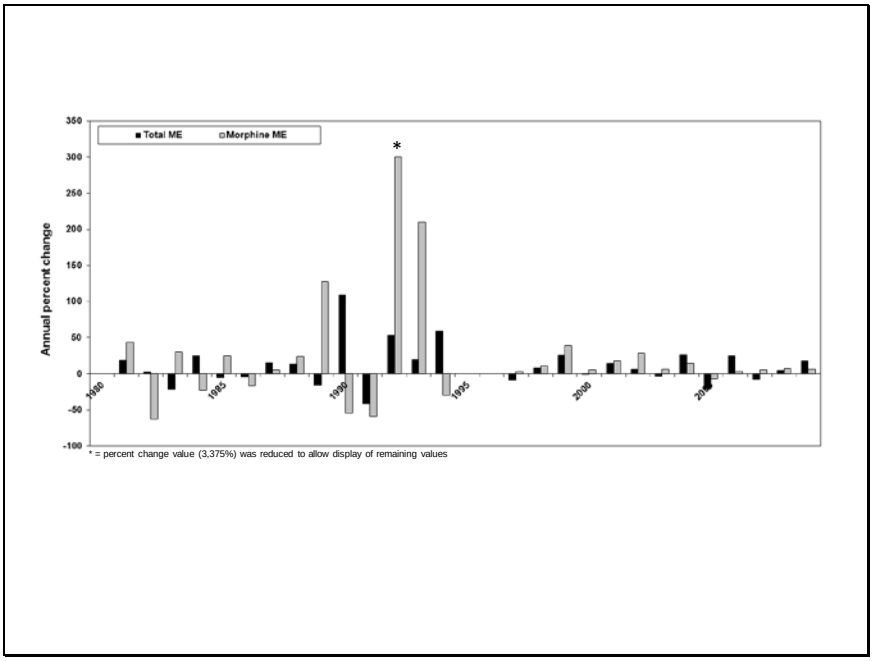
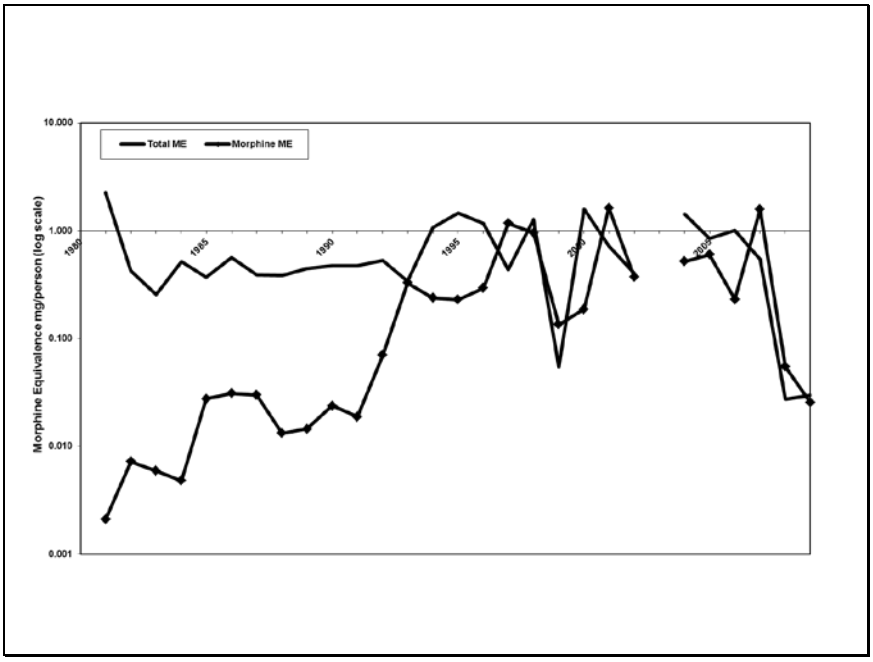


Figure 4d. (Botswana) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Africa Region



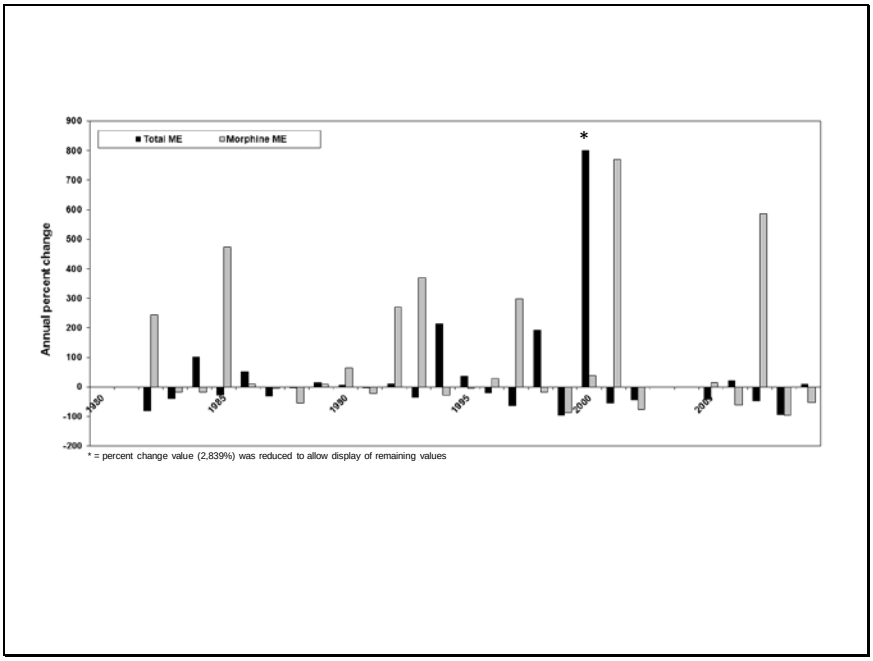
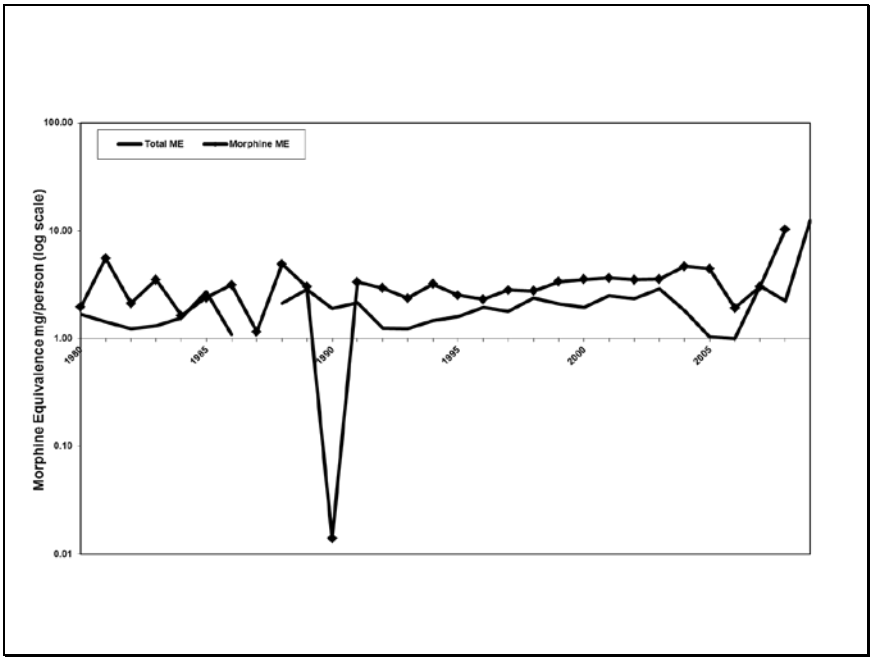


Figure 4e. (South Africa) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Africa Region



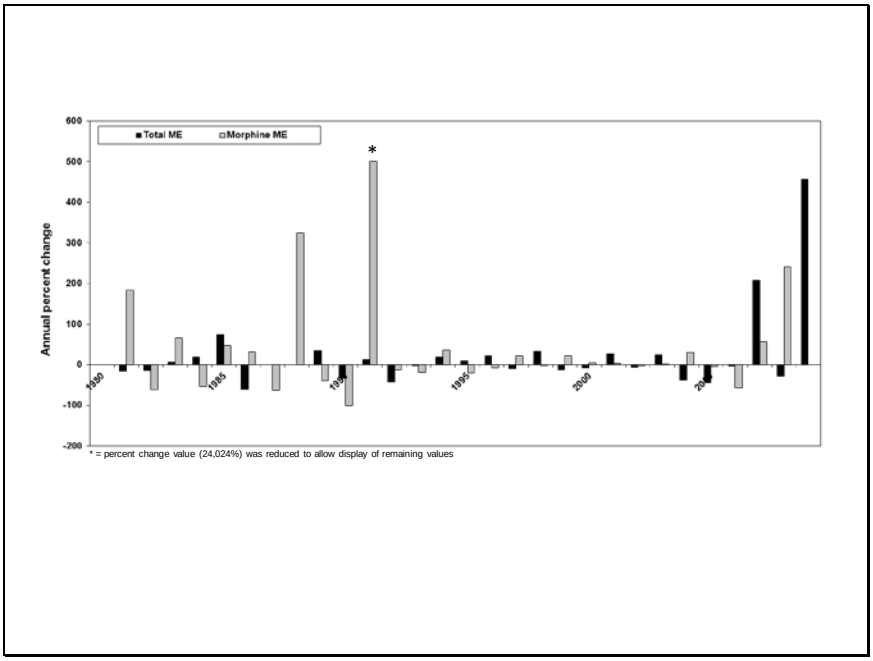
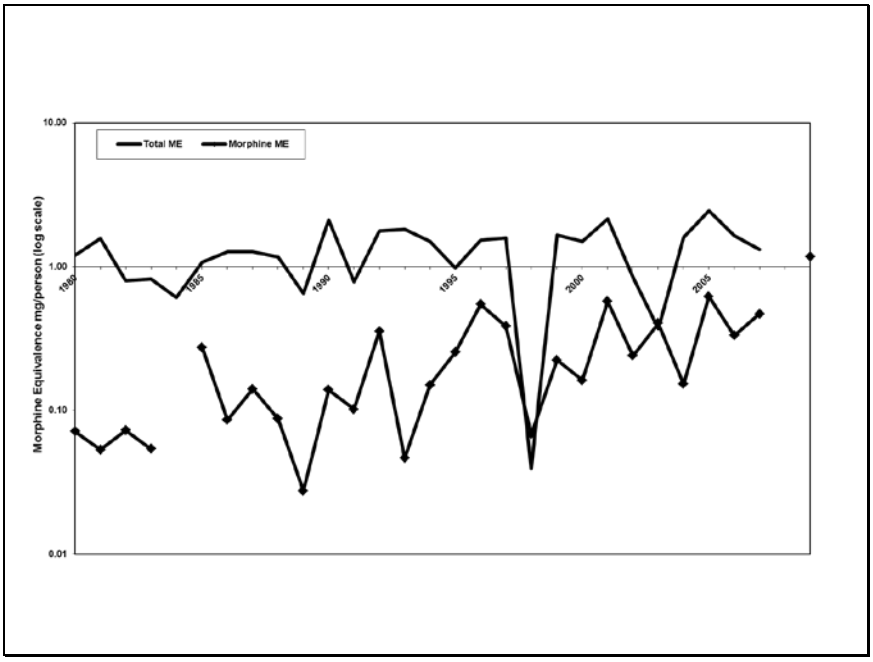


Figure 4f. (Mauritius) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Africa Region



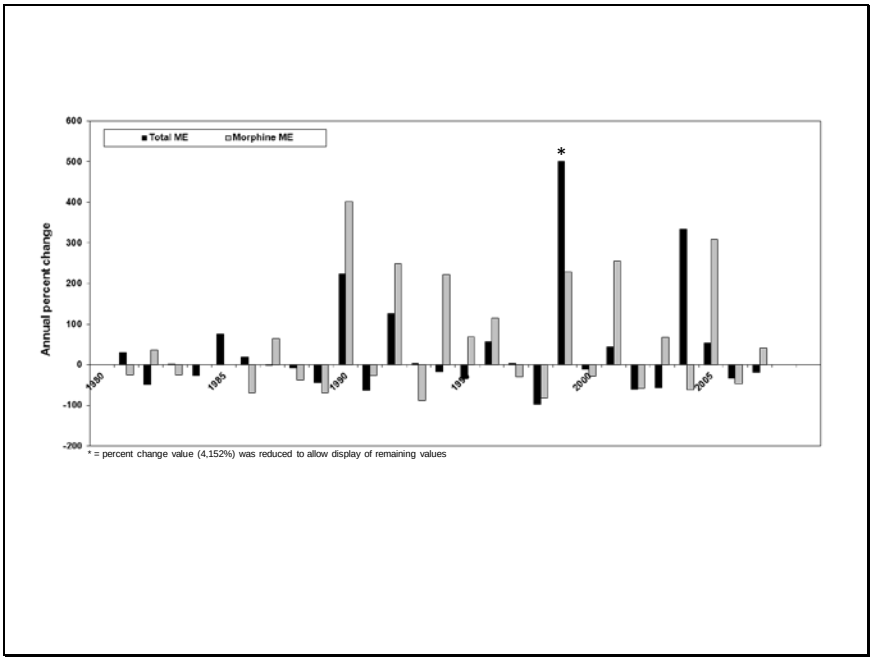
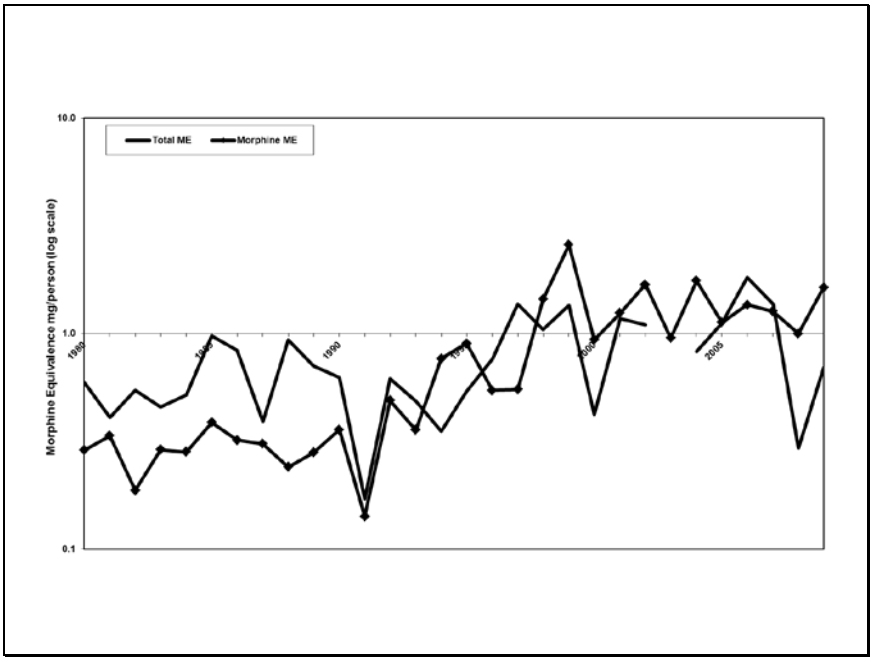


Figure 5a. (Cuba) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Americas Region



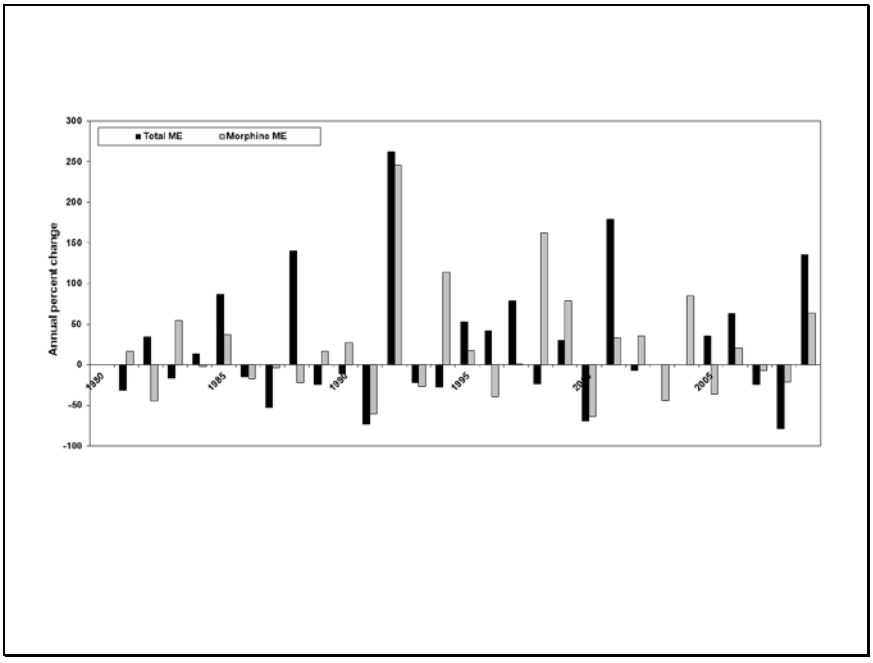
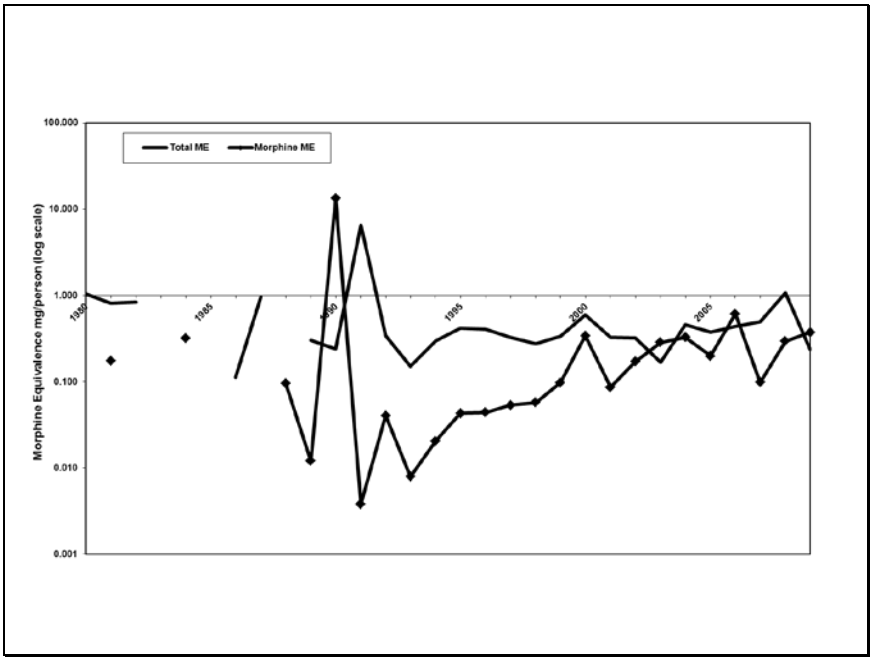


Figure 5b. (Nicaragua) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Americas Region



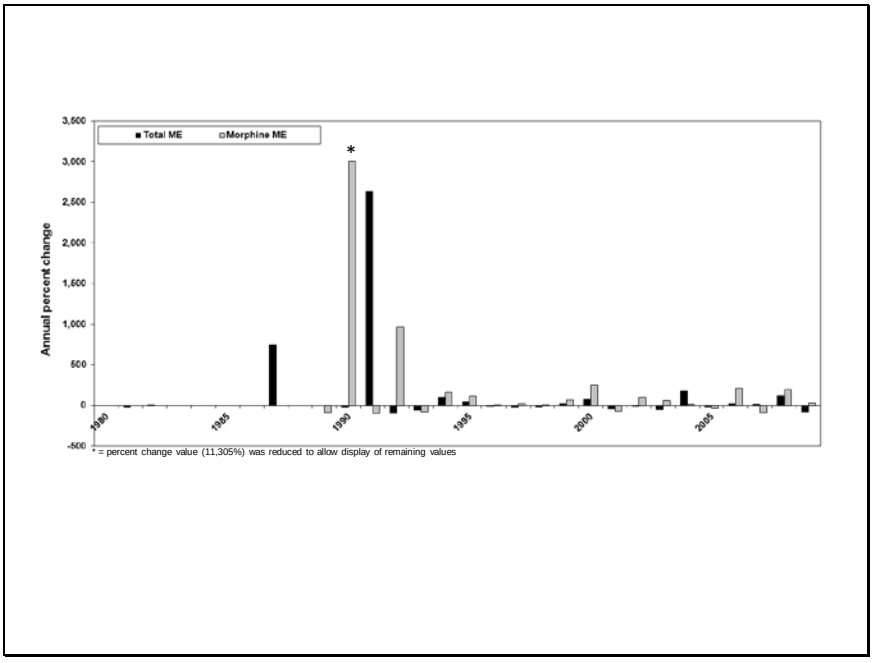
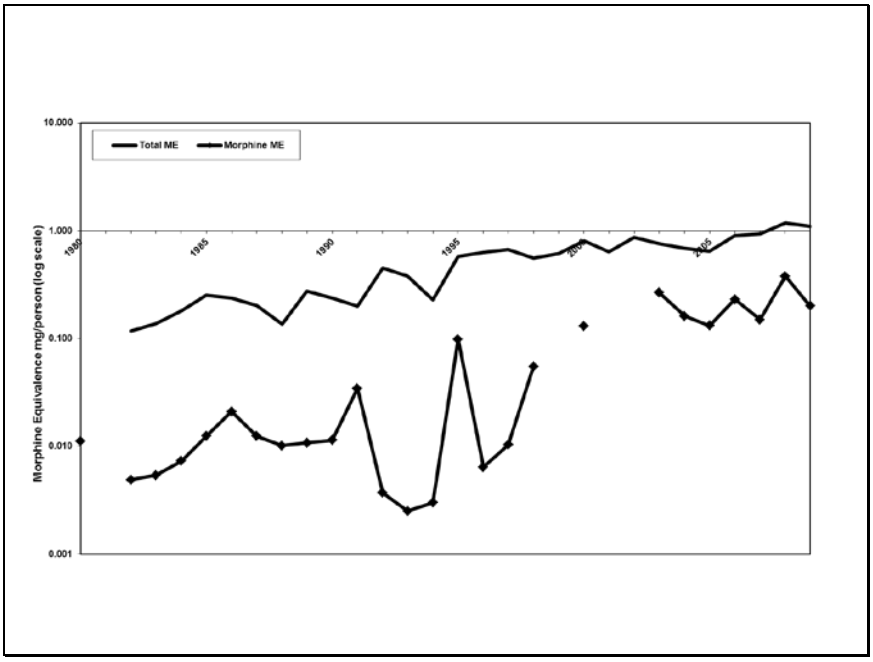


Figure 5c. (Ecuador) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Americas Region



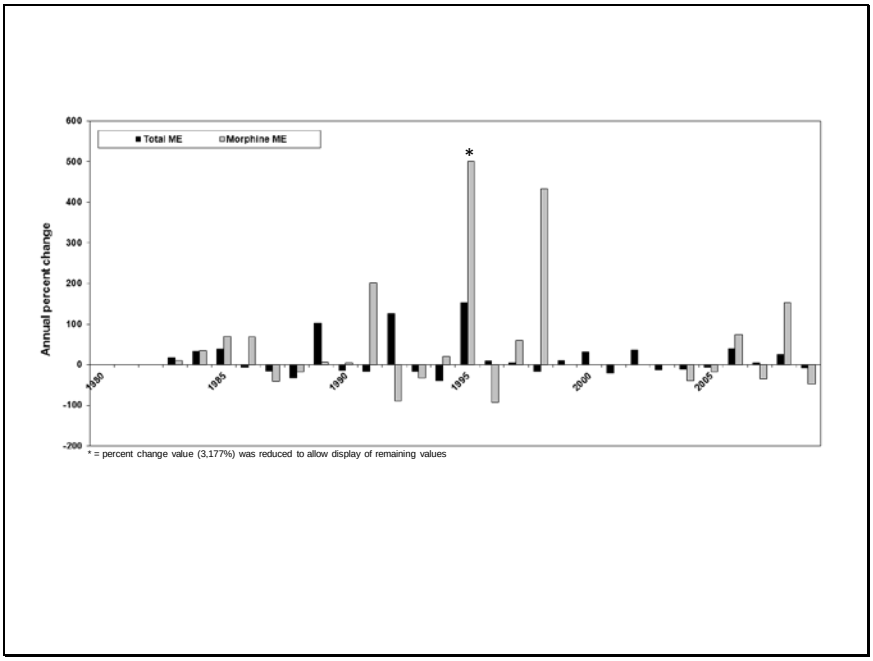
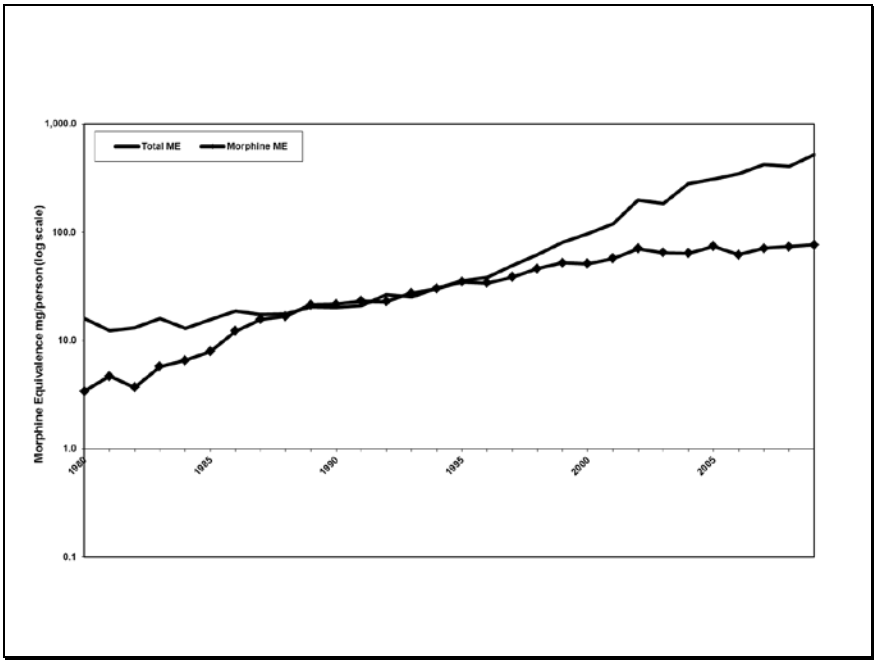


Figure 5d. (Canada) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Americas Region



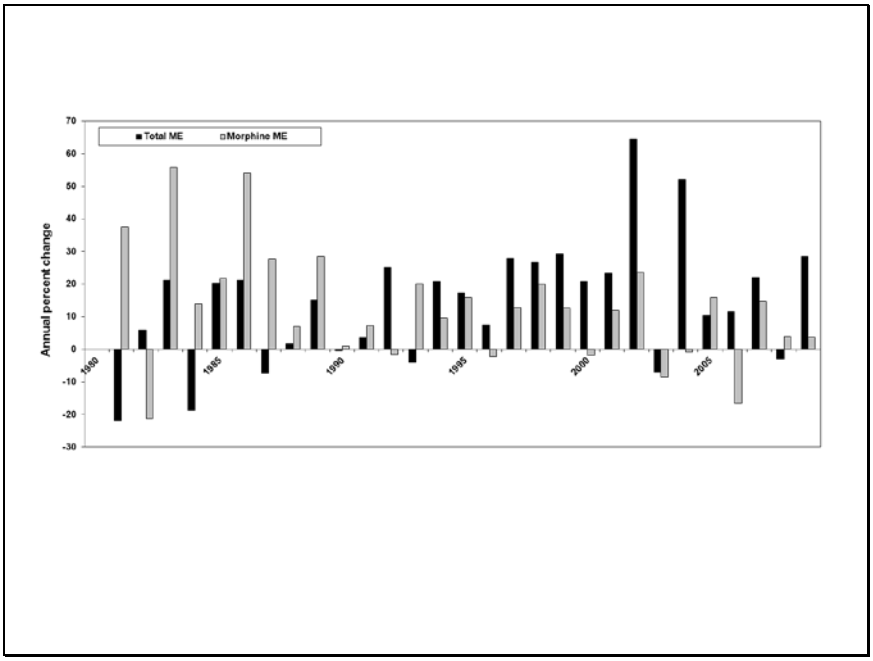
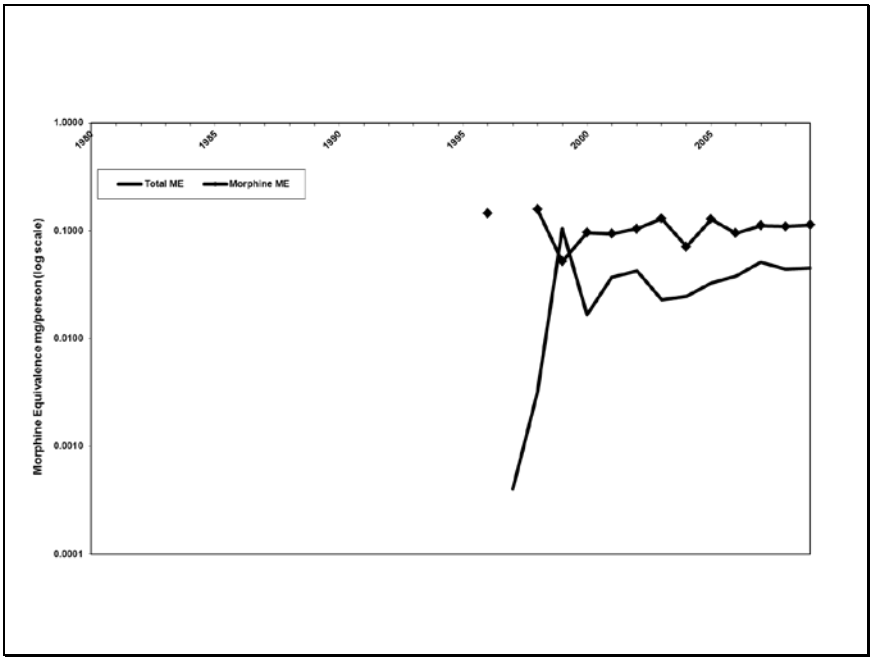


Figure 6a. (Uzbekistan) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Asia Region



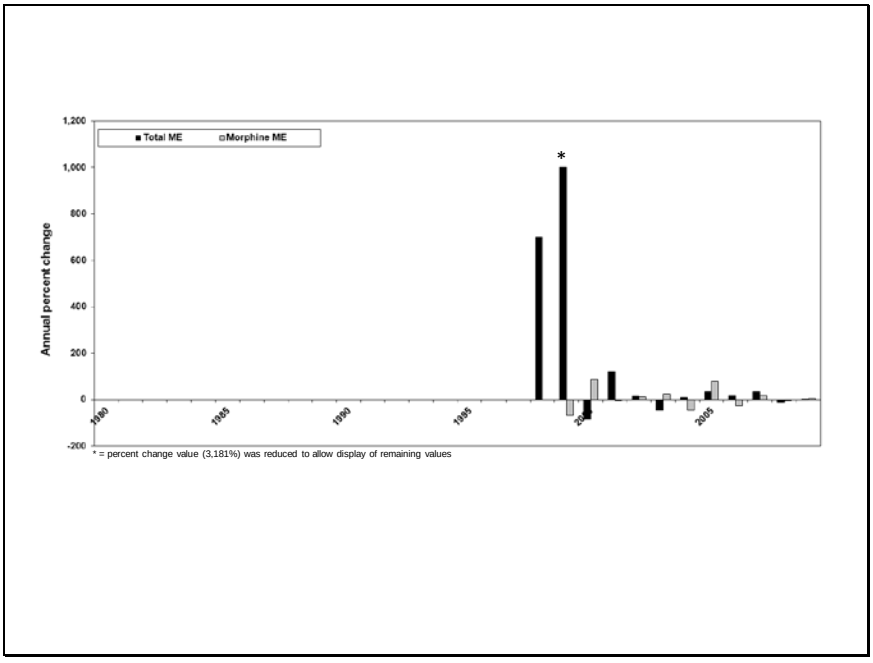
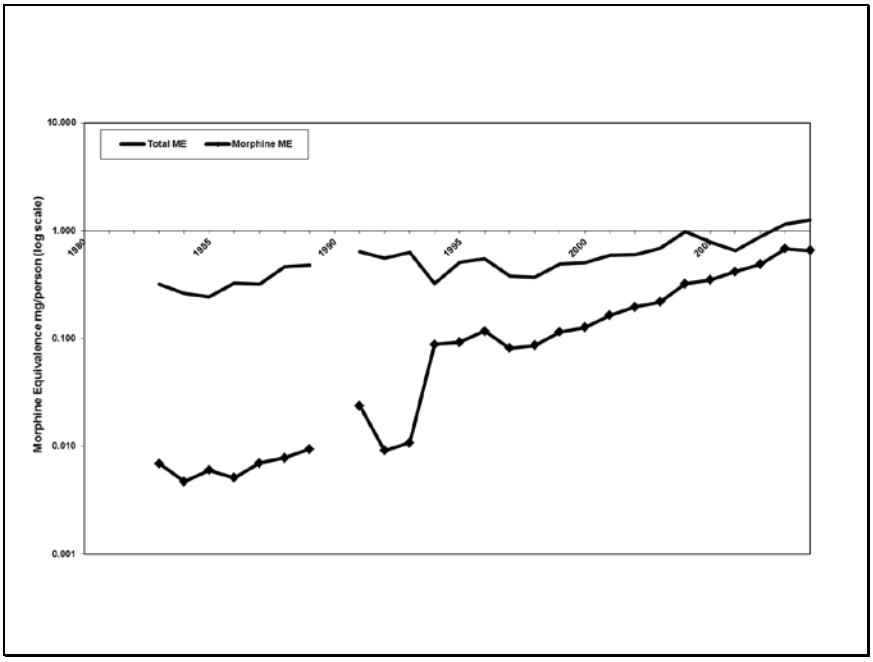


Figure 6b. (China) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Asia Region



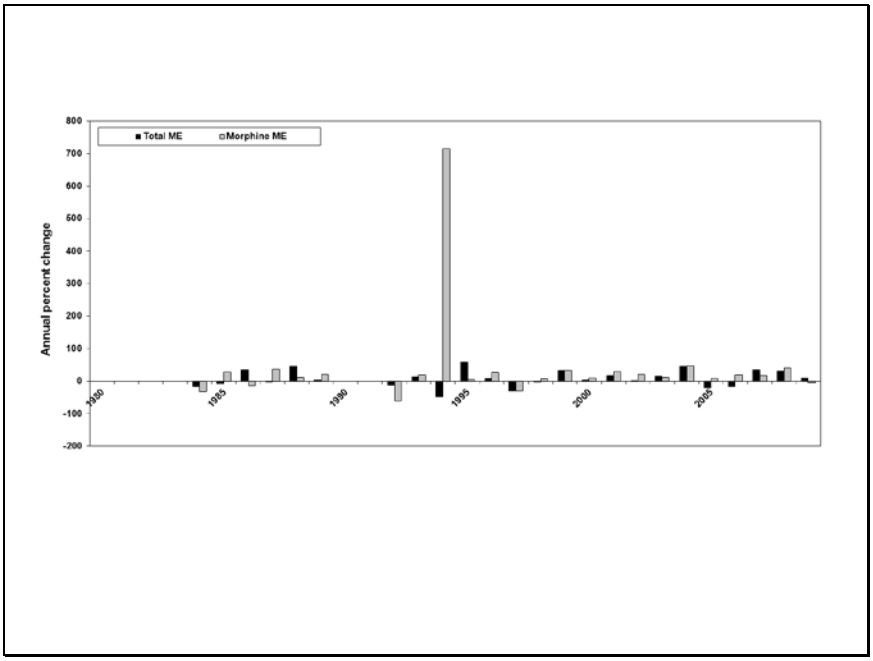
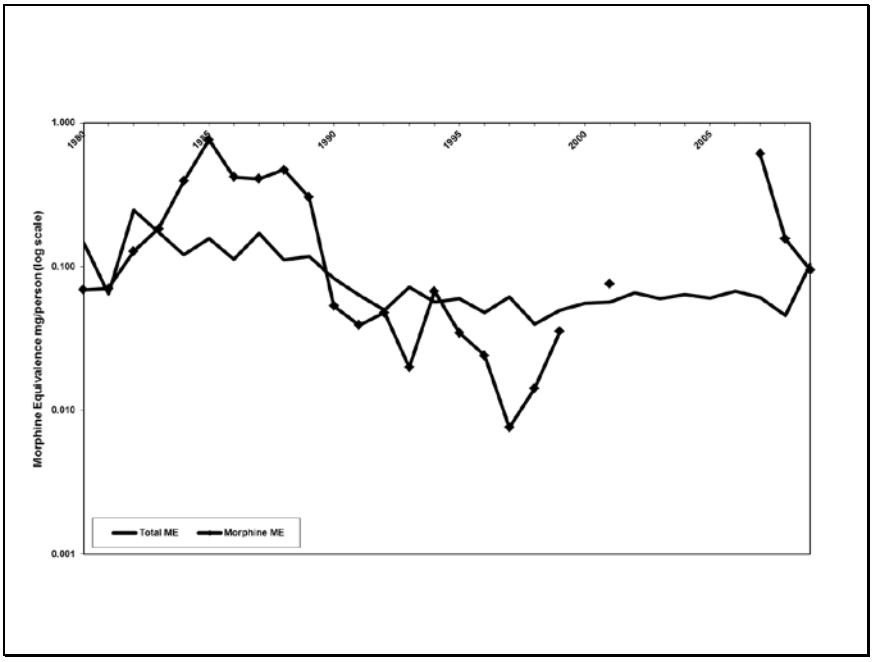


Figure 6c. (India) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Asia Region



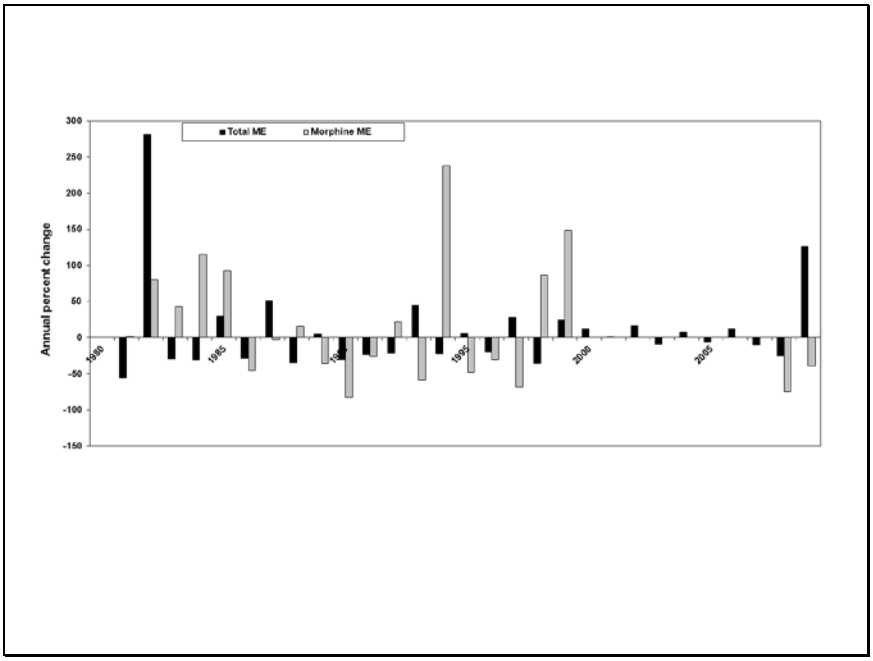
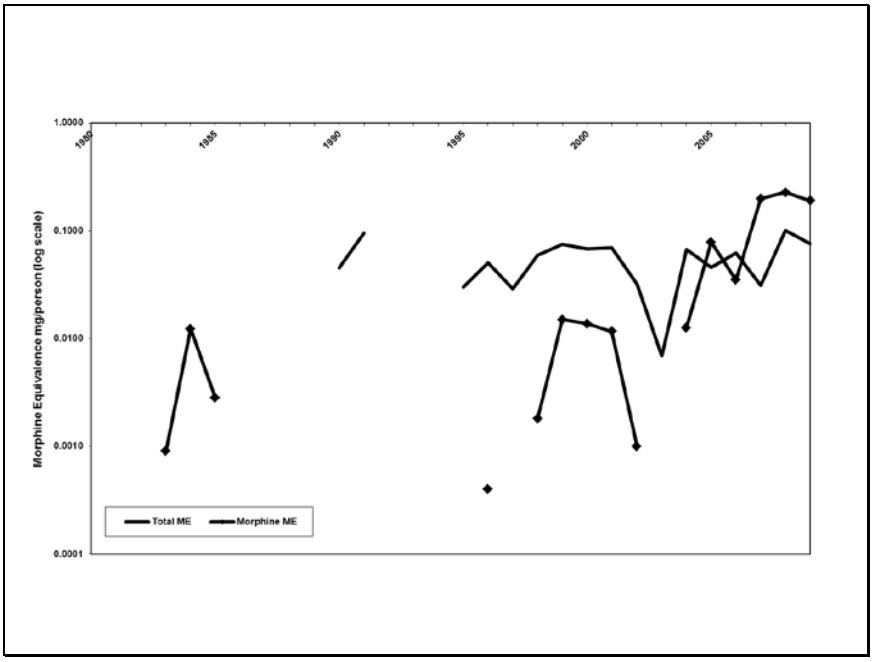


Figure 6d. (Nepal) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Asia Region



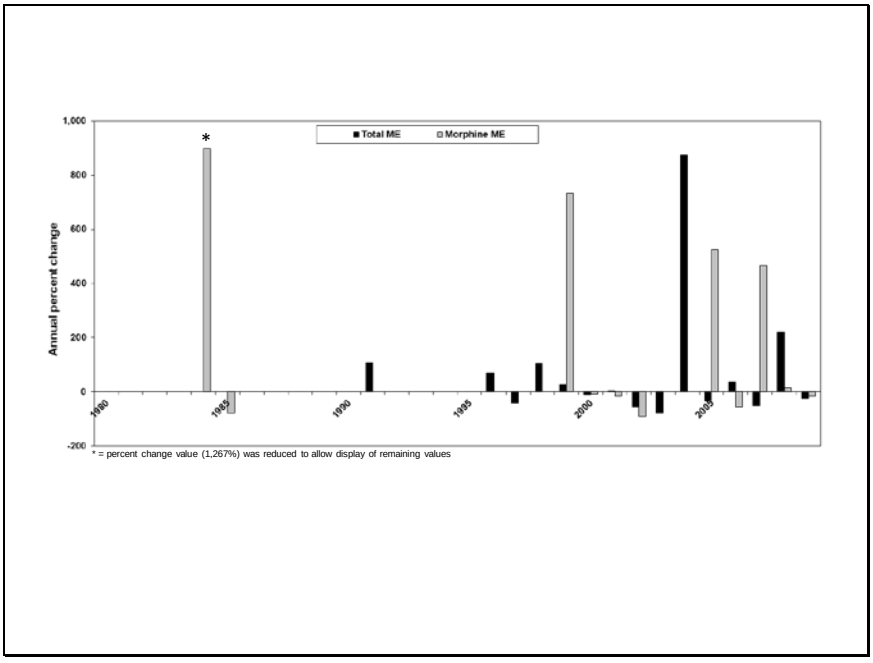
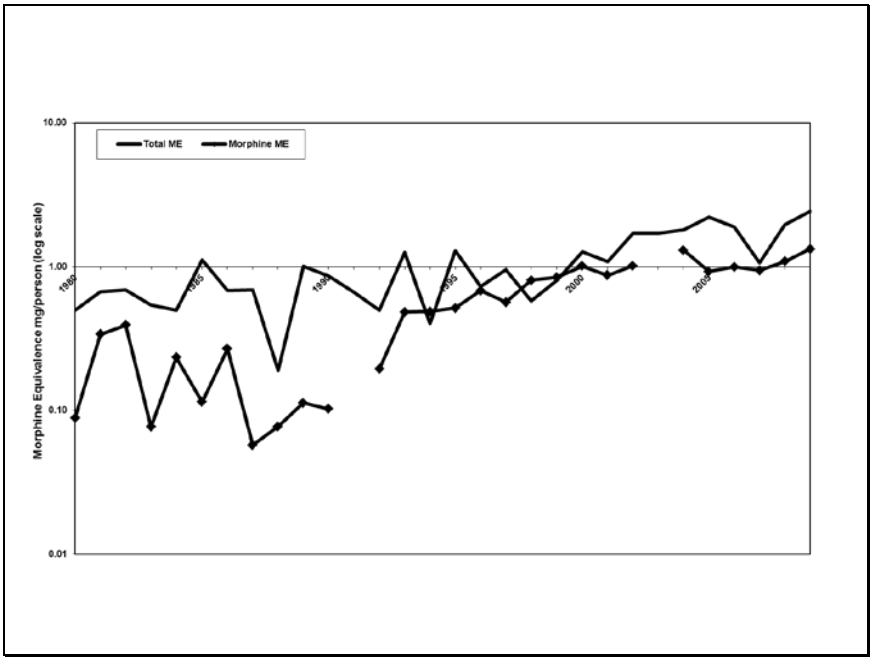


Figure 6e. (Malaysia) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Asia Region



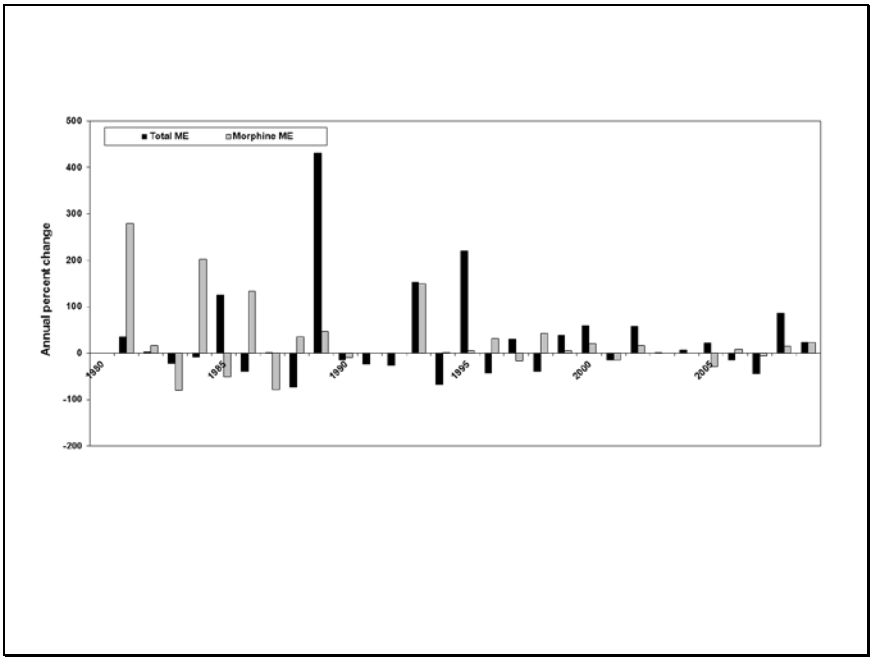
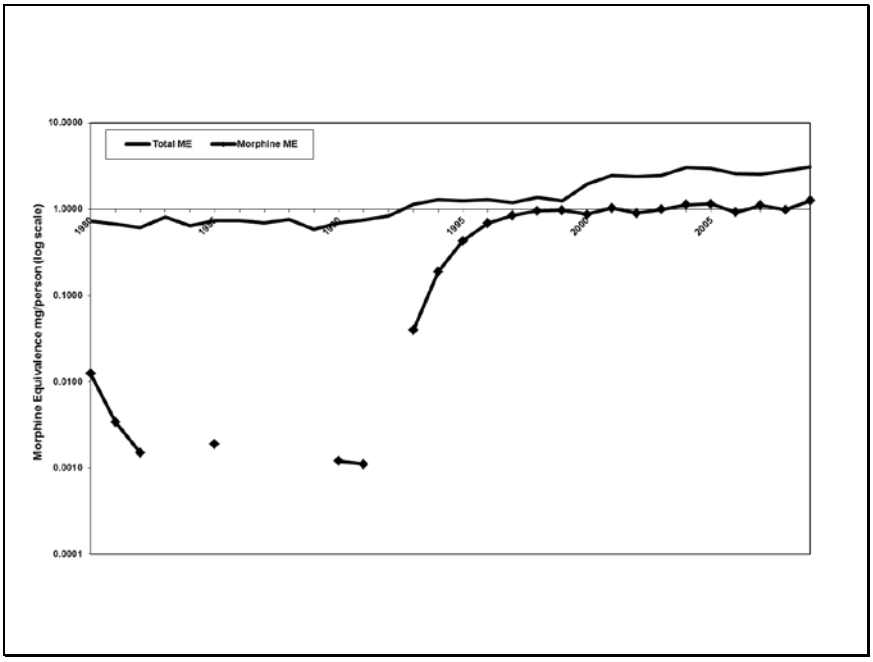


Figure 6f. (Lebanon) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Asia Region



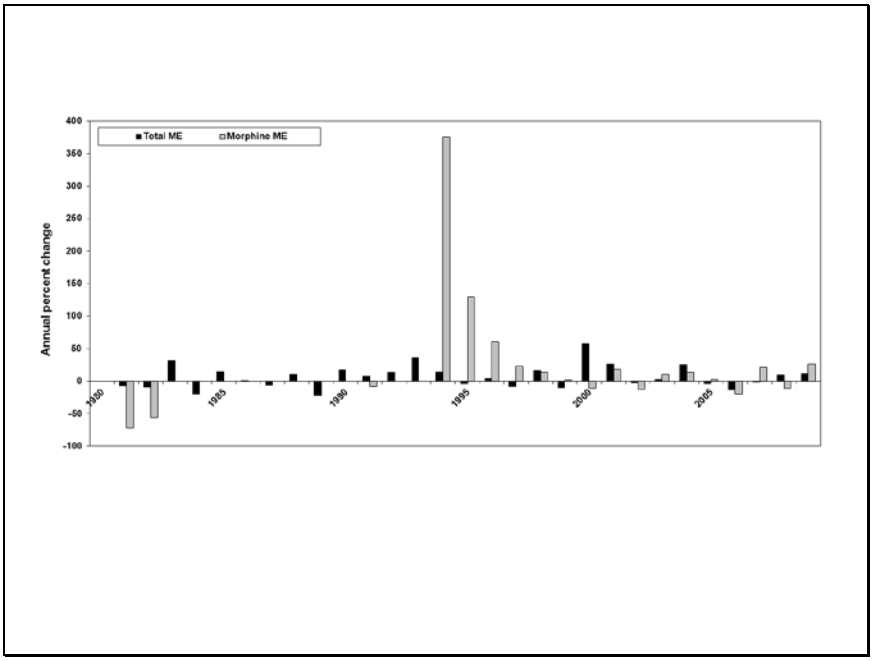
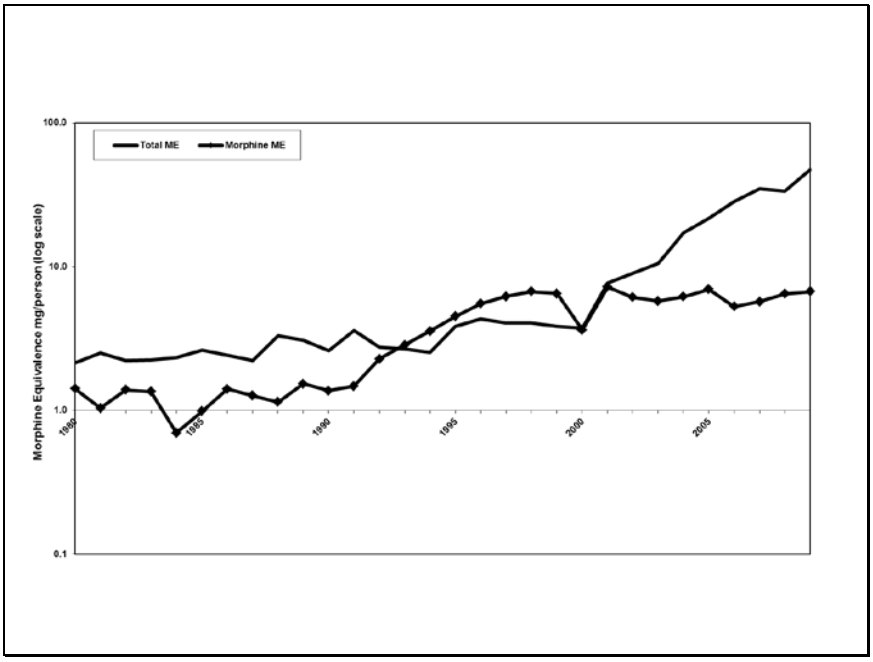


Figure 7a. (Poland) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Europe Region



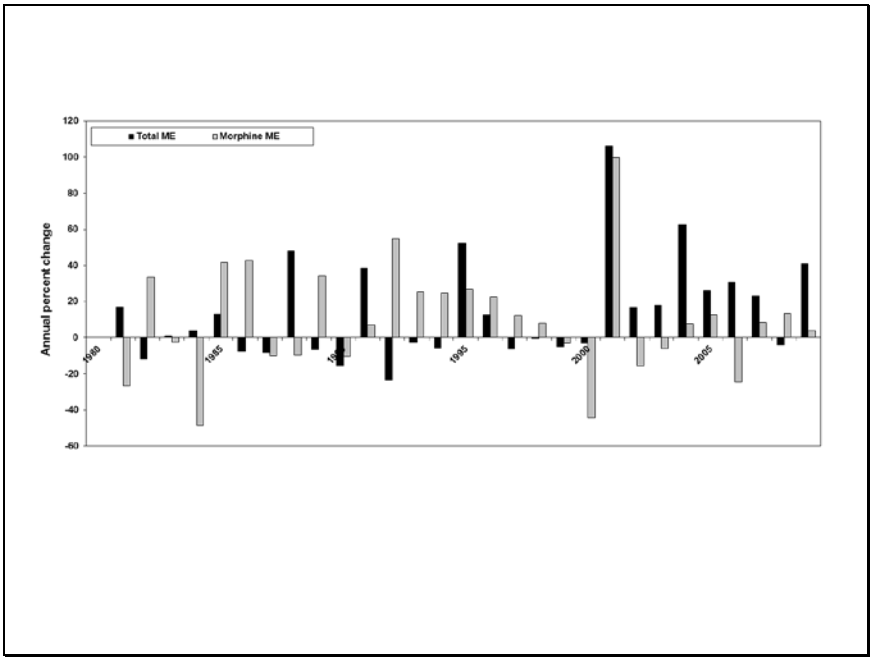
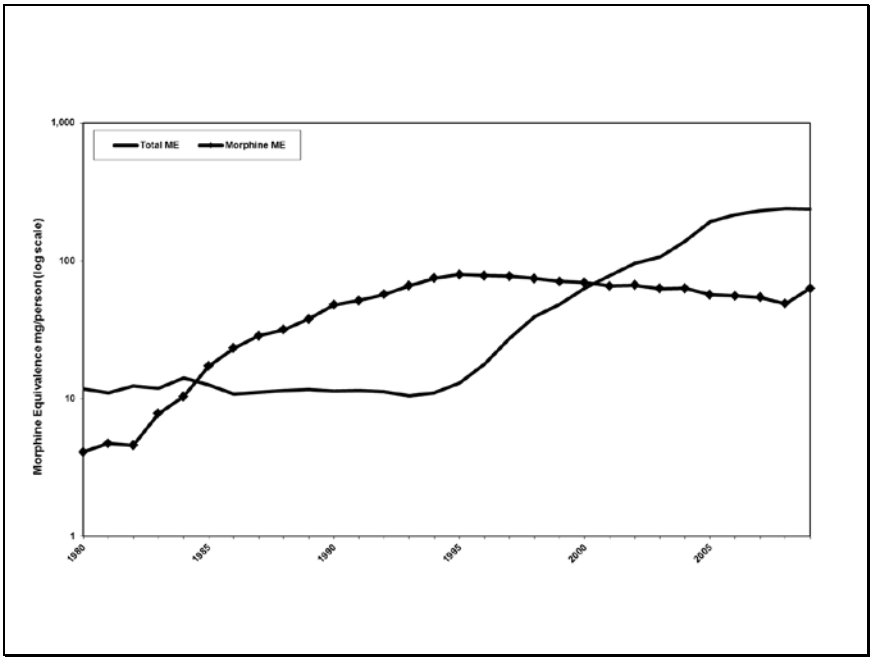


Figure 7b. (Denmark) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Europe Region



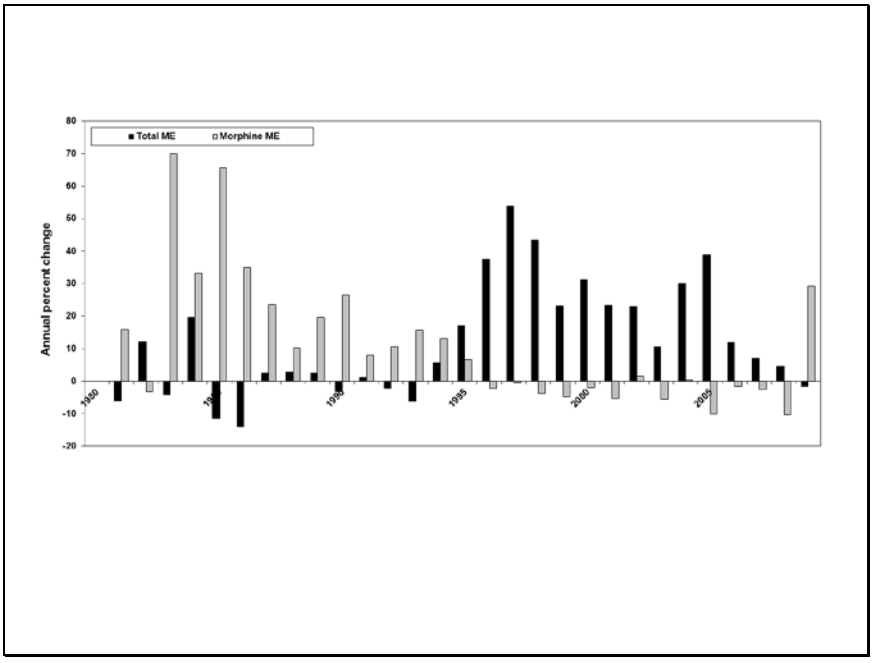
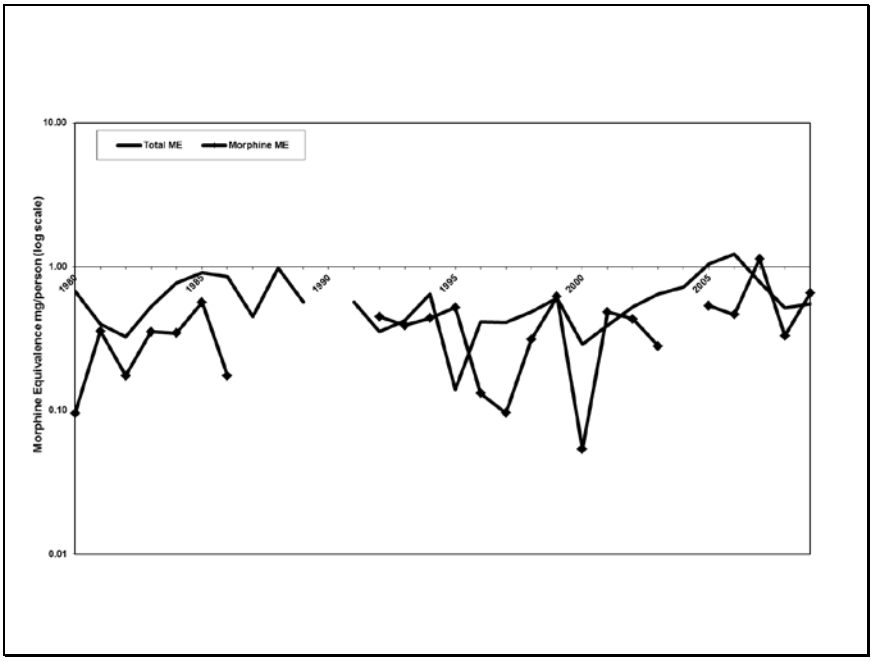


Figure 7c. (Albania) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Europe Region



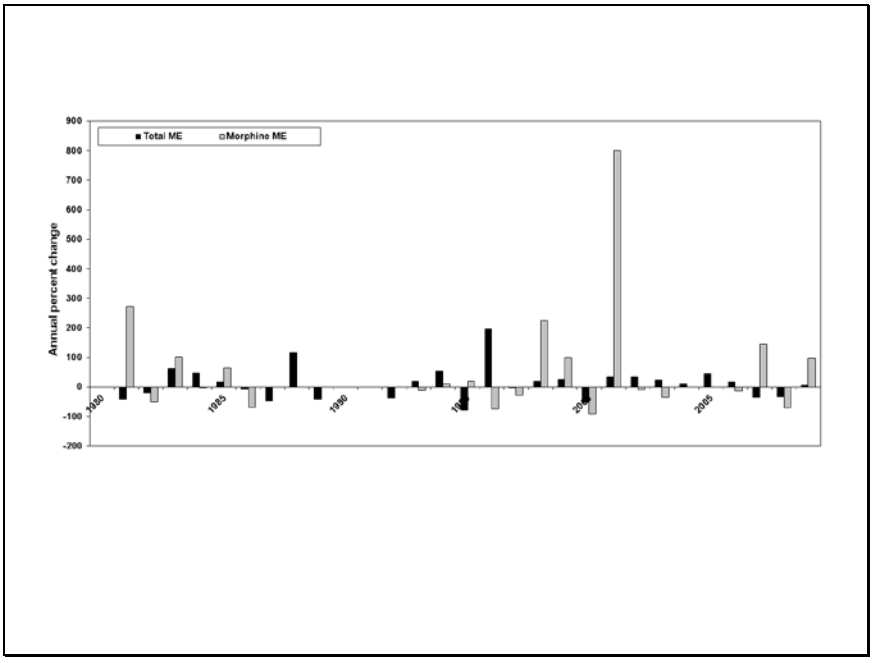
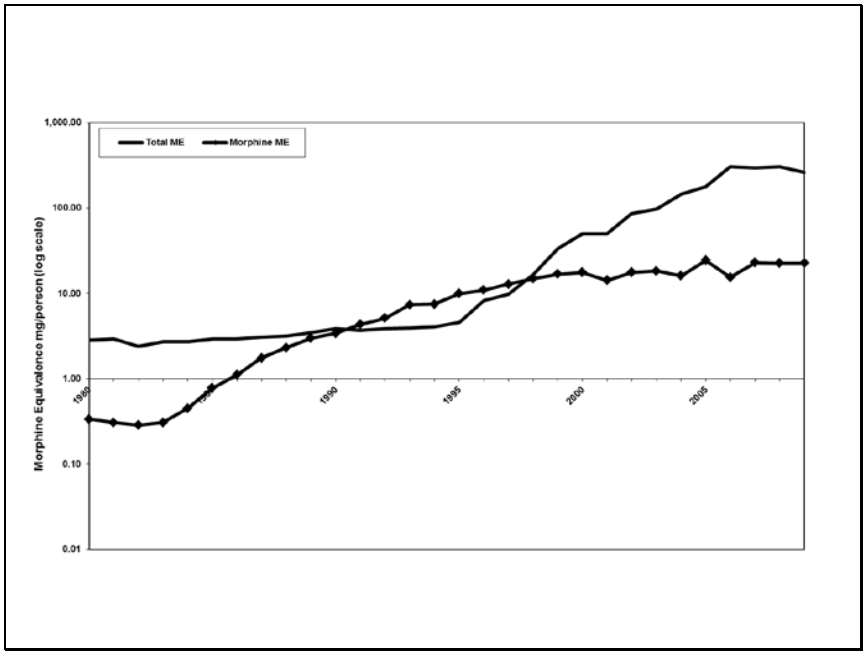


Figure 7d. (Germany) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Europe Region



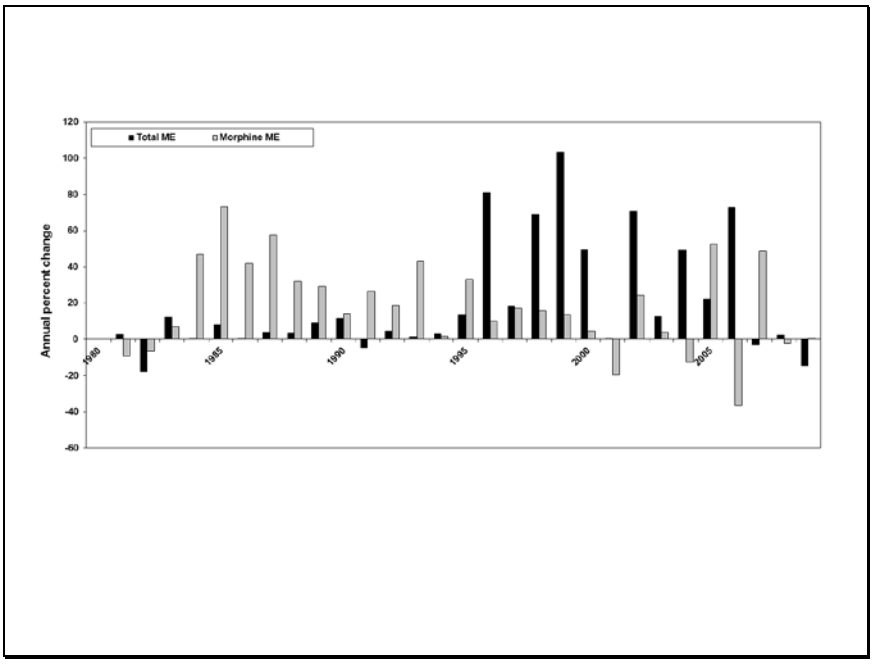
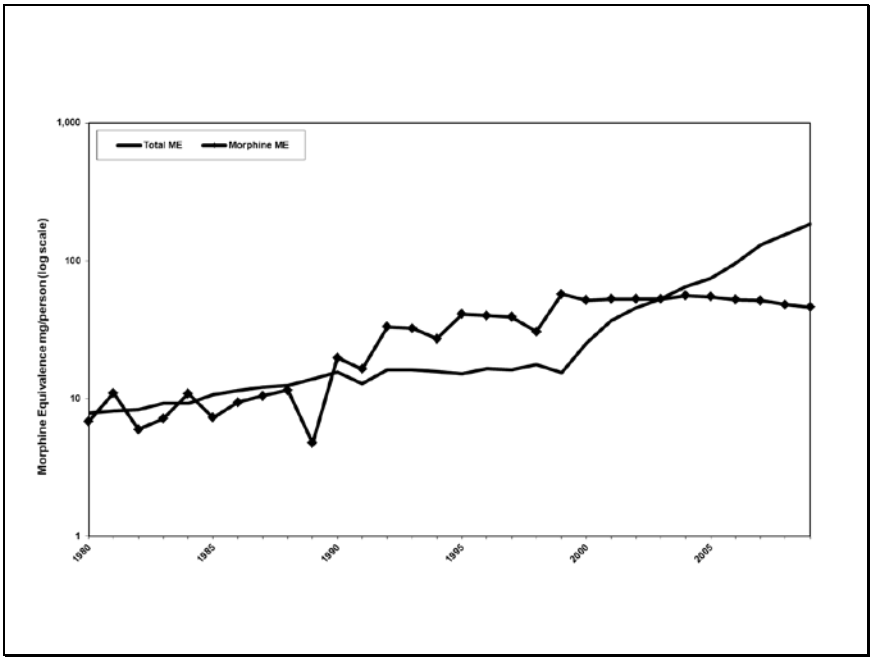


Figure 8a. Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Oceania Region



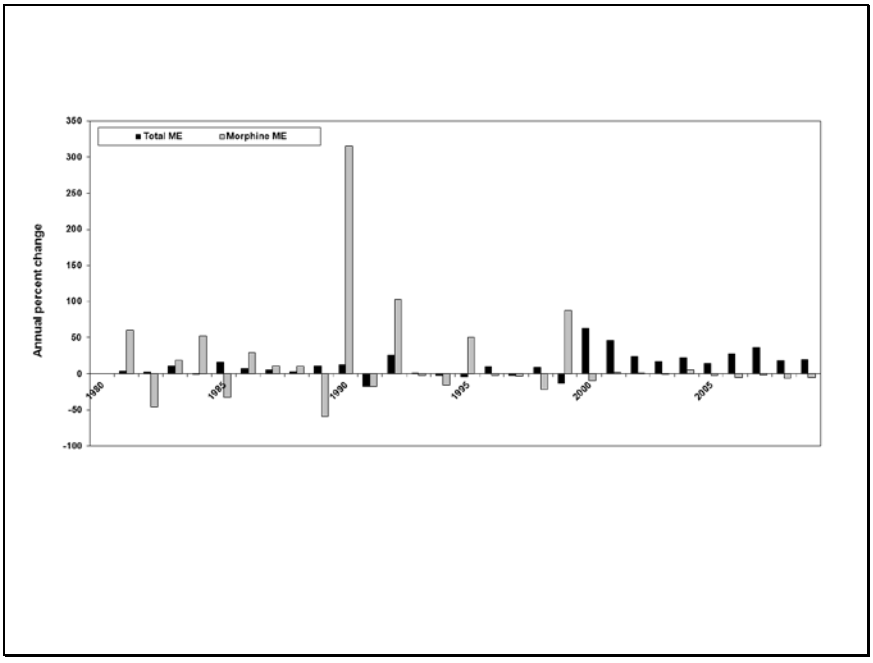
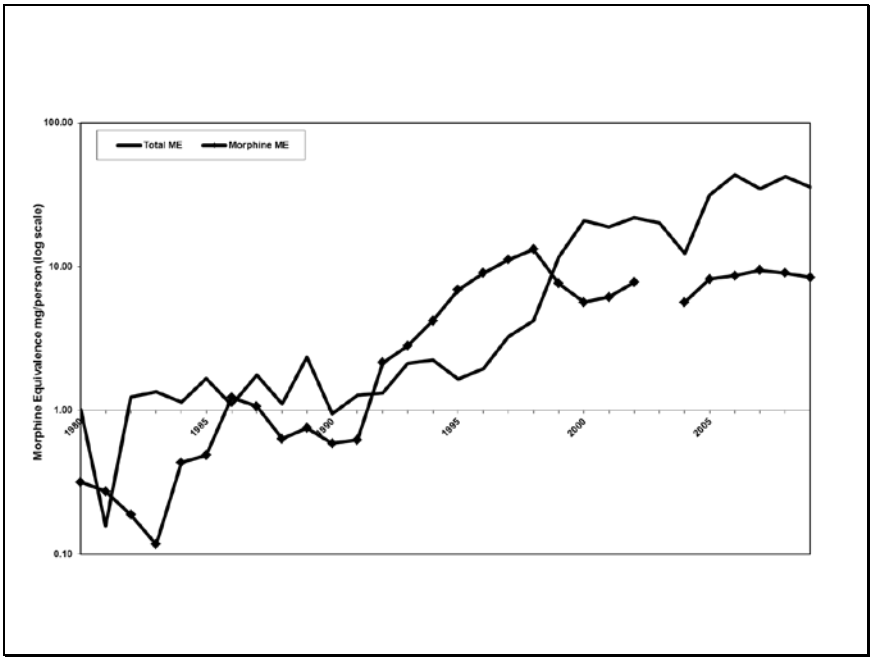


Figure 8b. (New Caledonia) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Oceania Region



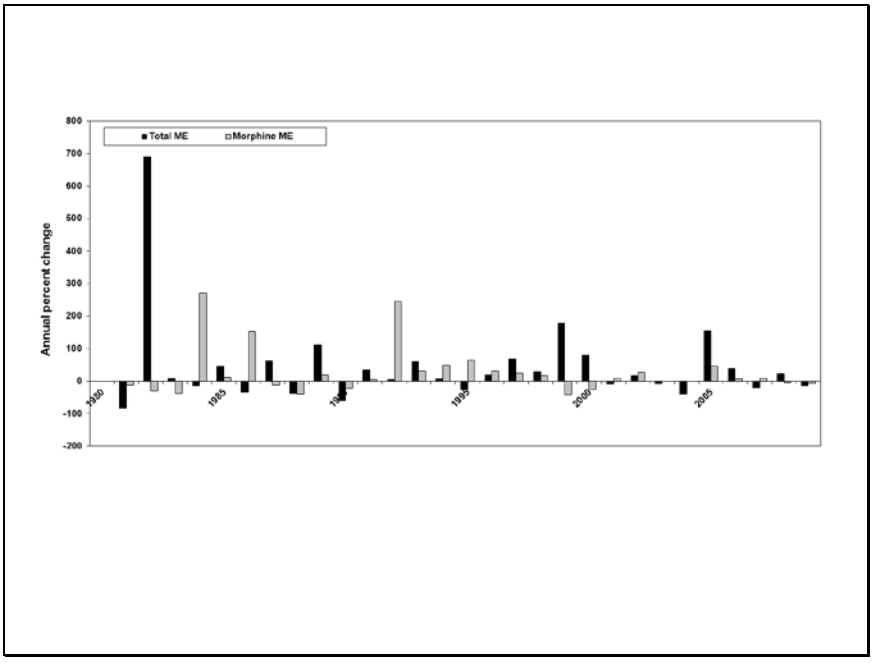
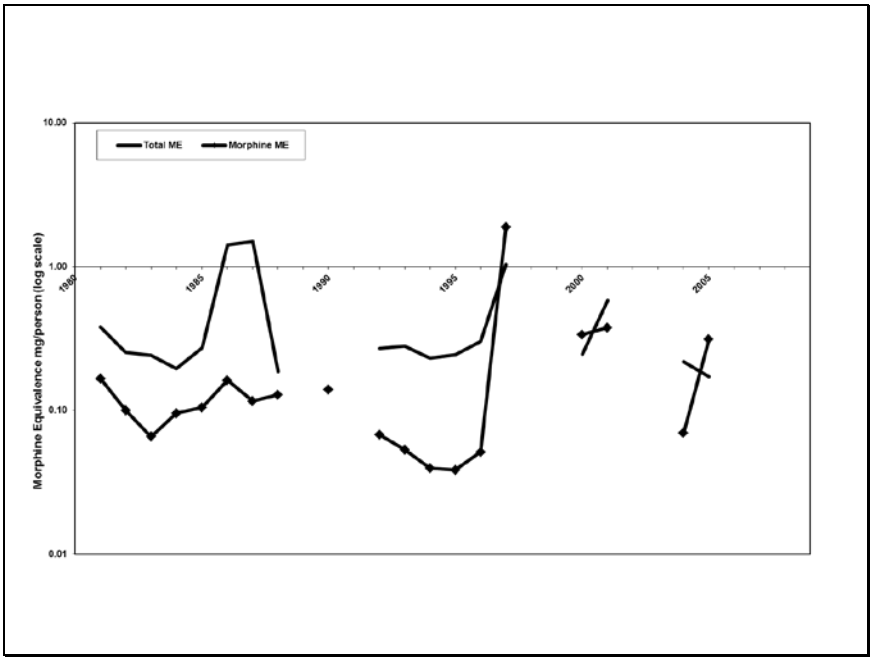


Figure 8c. Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Oceania Region



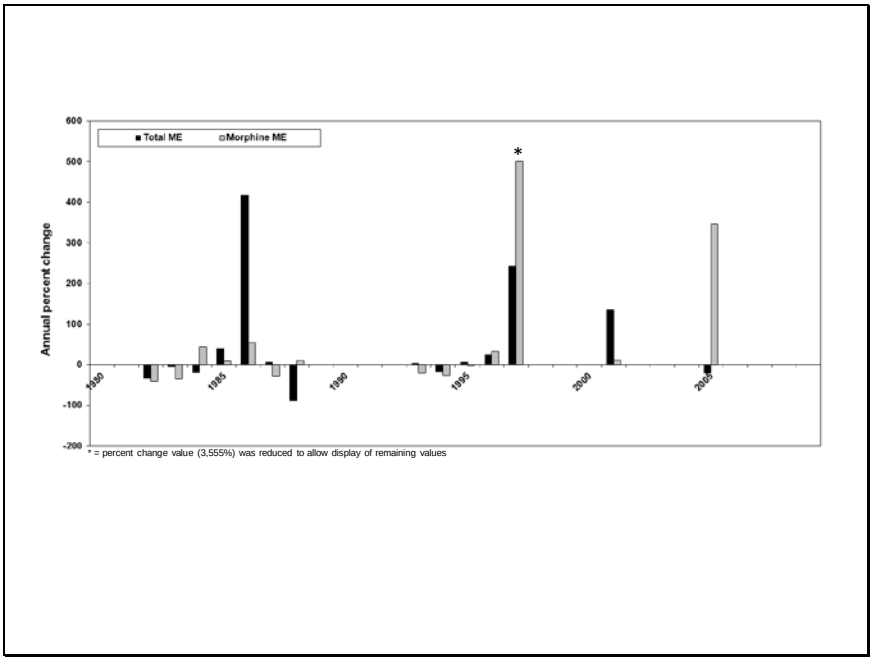


Figure 8d. (Cook Islands) Log Scale of Consumption Trends for Morphine and Total Morphine Equivalence (mg/person), in the Oceania Region