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## **Interim Safety Report on the Ruyan® e-cigarette**

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18 January 2008

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**Foreword**

This report is entitled an interim report, to permit further test results to be added as they come to hand. The company has allowed flexibility in the nature of investigations carried out. The tests reported are backed up by signed reports from the contracted laboratories. No completed test results have been withheld.

The Ruyan® e-cigarettes and the funds for testing them were supplied under a contract by SBT (Holdings) Ltd Hong Kong, but the findings are those of the author. Neither the author nor Health New Zealand Ltd holds stock in SBT (Holdings) Co. Ltd.



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**20 December 2007.**

**Summary**

The Ruyan® e-cigarette is designed to be a safe alternative to smoking, and on examination from a number of aspects, appears to achieve this aim. Its sophisticated electronics vapourizes, separately for each puff, very small quantities of *nicotine* dissolved in *propylene glycol*, two small well-known molecules with excellent safety profiles, – into a fine aerosol. Each puff contains one third to half the nicotine in a tobacco cigarette's puff. The cartridge liquid is tobacco-free and no combustion occurs. Once on sale, its on-going safety profile depends on 1) good manufacturing practice and pharmaceutical-grade purity of the nicotine and propylene glycol used in the cartridge liquid. 2) the prevention of shared use which could result in cross infection.

In early 2008, Clinical Trials Research Unit, University of Auckland is testing the e-cigarette's efficacy in raising blood nicotine levels and in reducing cigarette cravings.

- This report aims to assist regulators in initial assessment of the safety of the Ruyan® e-cigarette, and the possible risks and benefits from permitting its sale.
- Further tests are planned by Health New Zealand through to March 2008. The main direction of this report is, however, already clear.
- A number of e-cigarettes are on sale on the internet. This report is specific for the Ruyan® e-cigarette, manufactured by SBT (Holdings) Co. Ltd for Ruyan (formerly Golden Dragon) (Holdings) Co. Ltd, Hong Kong and Beijing. Their Ruyan® e-cigar and the e-pipe are similarly designed, but are not reported on here.

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## 1 Background

### 1.1 Risks of smoking

According to the World Health Organization, the annual death toll from tobacco smoking was 7.6 million world-wide in 2000, and rising.<sup>1</sup> Globally, smoking will soon exceed AIDS-HIV as the leading preventable cause of death.

Smoking multiplies the risk of dying early, doubling the risk for those who smoke 5 to 9 cigarettes a day, tripling the risk for smokers of 20 cigarettes a day, quadrupling the risk for smokers of over 25 per day.<sup>2</sup>

### 1.2 Separating nicotine from the smoke

Smokers smoke for nicotine but do not die from the nicotine<sup>3</sup> – they die from the smoke. *Smoking kills*, the warning on cigarette packets in many countries, is a precisely accurate statement.

Smoking kills because tobacco smoke contains cancer-causing tar solids (visible particles) in smoke, and certain known invisible toxicant gases such as butadiene (cancer-causing); hydrogen cyanide and carbon monoxide (affecting heart and blood vessels); and acrolein (damaging to the lungs).

Smoking tobacco is, until now, the only way to inhale nicotine into the lungs. The invention of the Ruyan® nicotine e-cigarette in 2004 is about to change that. The Ruyan® e-cigarette takes advantage of the fact that inhalation via a cigarette is the fastest route for nicotine absorption, and absorption by this route is 99% complete.

Before cigarettes were invented, lung cancer was unknown. People sniffed tobacco in the form of nasal snuff, or sucked or chewed it as oral snuff, instead of smoking it. Pharmacies today stock a range of nicotine products. Nicotine from patches is slowly and completely absorbed through the skin. The mouth mucosa filters out 60% of the nicotine in gum, lozenges and tablets, and absorption through the mouth can take half an hour. None of these methods allows the smoker to continue to enjoy the sensation of drawing on a cigarette to get the nicotine.

### 1.3 Stopping smoking only way to prevent smoking deaths in next 20 years

- As almost all tobacco smoking deaths occur at age 35 years onwards,<sup>4</sup> those smokers who will die of smoking in the next 20 years, are already smokers – and their deaths can only be averted if they can be persuaded to stop smoking. Stop smoking can be either by quitting smoking entirely, or switching to a non-tobacco smoking product.

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<sup>1</sup> Tobacco Atlas. World Health Organization. [www.who.int/tobacco/en/atlas11.pdf](http://www.who.int/tobacco/en/atlas11.pdf)

<sup>2</sup> Bjartveit K, Tverdal A. Health consequences of smoking 1-4 cigarettes per day. *Tobacco Control* 2005; 14: 315-20, based on follow-up of 43,000 Norwegians from 1970s to 2002.

<sup>3</sup> Murray RP, et al. Safety of nicotine polacrilex gum used by 3094 participants in the Lung Health Study. *Chest* 1996; 109: 438-45. Followed for 5 years, compared with 1900 controls. No increase in hospitalization or mortality was found in the nicotine gum chewers, whether still smoking or not.

- Unfortunately, even world-leading programmes to reduce smoking (such as New Zealand's) are succeeding only slowly, so that, by promoting quitting alone, smoking will take another 70 years to reach zero.
- A large part of the problem is that many smokers are unwilling to quit their addiction to nicotine. The Ruyan® e-cigarette provides an easier escape route for smokers.
- WHO has recommended that alongside the individual approach (including pharmacological interventions), a supportive (policy) environment is needed, and recommends “a broad framework for addressing smoking cessation and treatment of tobacco dependence.”<sup>4</sup>
- Such a framework would logically permit widespread sale of a range of cigarette substitutes that each provided “clean” nicotine for lung inhalation.

### 1.4 Life years reclaimed if smokers switch to smoking the Ruyan® e-cigarette

Here we estimate the public health benefits of widespread adoption of the Ruyan® e-cigarette *or any other product, policy or programme* that can likewise persuade smokers to stop smoking without adding any extra risk.

**At personal level.** For every two continuing smokers, one will die early from smoking (on average 13 years early<sup>5</sup>). So if two smokers both switch to e-cigarettes from the beginning, or otherwise succeed in quitting smoking, then 13 life years will be reclaimed.

**In percentage terms.** Similarly, for every 100 continuing smokers, 50 will die early from their smoking (on average dying 13 years early)<sup>6</sup> If, however, all 100 switch to e-cigarettes (or otherwise stop smoking tobacco) before 35 years of age, we would expect that 50 fewer will die early, a total of 650 life-years reclaimed, per 100 smokers. This is based on the proven zero excess mortality effect from daily use for five years of nicotine without tobacco.

**At country level** For New Zealand, with 21% of adults smoking and 656 000 daily smokers,<sup>7</sup> 4.3 million life years would be saved, in country of 4.2 million population, or one life-year reclaimed per capita, if everyone stopped smoking; equal to increasing life expectancy by one year averaged over the entire population. In reality, it is the smokers who stop smoking by abstinence or switching to the e-cigarette, who obtain this gain in longer life.

## 2. Description

The Ruyan® (pronounced Roo yen) (e for electronic) cigarette, like a tobacco cigarette, can rapidly deliver nicotine into the lungs, but without smoke carcinogens and toxicants.

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<sup>4</sup> da Costa e Silva V. Policy recommendations for smoking cessation and treatment of tobacco dependence. Tools for Public Health. World Health Organization 2003. 107 pp. ISBN-13. 9789241562409.

<sup>5</sup> Peto R, Lopez AD, Boreham J. et al. Mortality from smoking in developed countries, 2004. [www.ctsu.ox.ac.uk](http://www.ctsu.ox.ac.uk) New Zealand data.

<sup>6</sup> Peto R, Lopez AD, Boreham J. et al. Mortality from smoking in developed countries, 2004. [www.ctsu.ox.ac.uk](http://www.ctsu.ox.ac.uk)

<sup>7</sup> New Zealand Census March 2006. Smoking prevalence 20.7%. [www.statistics.govt.nz](http://www.statistics.govt.nz)

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The Ruyan® e-cigarette was first sold in May 2004, in China, with annual sales since of around 300,000 per year, and advertising on television, but no adverse effects reported by the English language dailies in China. Its December 2007 internet price was around US \$208, with nicotine cartridge refills required every 300 puffs (1-4 days) costing extra. After 1300 puffs the battery is recharged from the mains.

## 2.1 Structure.

The distal segment with a red light indicating inhalation, contains the re-chargeable battery and is the controlling part. The middle part contains a vaporising chamber. The mouthpiece and nicotine cartridge are one piece, and a new one is inserted after 300-350 puffs. The nicotine in the cartridge is dissolved in propylene glycol (PG).

## 2.2 Function.

The e-cigarette is flameless and non-flammable. The pressure sensor in the controlling part electronically initiates rapid vaporisation of a dose of liquid propylene glycol containing nicotine into a fine aerosol that reaches the lung rapidly.<sup>8</sup> The dose per puff depends on the volume and force of the inhalation, and the number of puffs determines total dose.

## 3. Nicotine effects

The safety and toxicity of nicotine has been exhaustively reviewed.<sup>9</sup> The safety of pure nicotine alone, relative to tobacco smoking is not in question, nor is its overall safety in absolute terms. Death has been recorded occasionally from accidental poisoning from nicotine (Section 7), but not from medicinal use.

No nicotine poisoning effects have been reported for the e-cigarette. In contrast to the use of alcohol or oral snuff, the very rapid absorption enables the user to become aware of the first effects (light-headedness, queasiness) before serious overdosing can occur.

### 3.1 Short-term effects

**Dose-control.** For each puff, “what you inhale is what you get”. The smoker is protected from unwanted nicotine by the electronic circuitry shutting off almost immediately after each puff is taken. The smoker controls the size of the puff which determines the nicotine dose. The strength of the dose is immediately and correctly signalled by the irritation to the back of the throat, as no menthol is used to anaesthetise it. Thus the smoker is able to accurately control the dose from puff to puff.

With a zero-nicotine e-cigarette, there is no harshness on the throat, and without such negative feedback, the smoker may puff more frequently, but no nicotine can be inhaled. Purchasing 16 mg, 11 mg, 6 mg or 0 mg nicotine strengths of cartridge provides another way in which e-cigarette smokers can pre-regulate their nicotine intake.

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<sup>8</sup> Hon, Lik. China. A non-smokable electronic spray cigarette. Patent CA 218174, published 2004/03/08.

<sup>9</sup> Nicotine Safety and Toxicity. Ed. NL Benowitz. Oxford. OUP. 1998.

**Efficiency.** No nicotine is wasted in the e-cigarette— over one to four days its nicotine is eventually all inhaled, thus differing from the 12% uptake of nicotine from the tobacco cigarette. In the tobacco cigarette, after combustion, most is lost in side-stream smoke. Of the mainstream smoke some is entrapped in the cigarette filter, while only 1.5 mg (12%) of the cigarette’s original nicotine content of 13 mg is inhaled. (Table 1).

**In first-time smokers.** Acute nicotine toxicity occurs when never-smokers smoke their cigarette (whether tobacco or e-cigarette), becoming light-headed, with nausea and even vomiting, lasting typically for half an hour. Many would-be smokers are thus discouraged from learning to smoke.

**Maintenance of steady nicotine blood levels.** The experienced smoker of the e-cigarette controls the nicotine intake to maximise pleasure and minimise discomfort. A regular e-cigarette or tobacco cigarette adjusts the size or frequency of each subsequent puff, to maintain nicotine blood levels high enough to avoid unpleasant craving for a cigarette, and low enough to avoid excessive harshness on the back of the throat, or light-headedness due to a high blood level of nicotine.

**Self-medication.** In a relaxed situation, a smoker may deliberately inhale to achieve the nicotine rush or buzz or light-headed feeling, which will pass within half an hour or so. This is nicotine self-medication, or drug-effect seeking behaviour, which many smokers practice. Inhaling to the point of light-headedness can be harmful for tobacco smokers, tobacco snuff users and e-cigarette smokers who have to drive a car or operate heavy machinery immediately afterwards.

**3.2. Long term effects.** Thousands of smokers and former smokers have used nicotine in the form of gum for five years with no increase in mortality or hospitalisation.<sup>3</sup>

**Longevity** The cumulative excess risk of continuing to smoke tobacco cigarettes beyond age 35 years is one in two.<sup>2</sup> As the e-cigarette carries no risk to longevity, the average smoker switching to the e-cigarette before age 35 years will reduce their risk of dying early by one in two.

**Cancer and Cardiovascular toxicity.** Nicotine is not a cause of cancer. The tendency for nicotine to temporarily increases heart rate and blood pressure flattens out above 8 mg yield per cigarette, so that low doses produce much the same effect as high doses,<sup>6</sup> suggesting that nicotine does not cause cardiovascular toxicity.

**3.3 Previous tobacco smoking puts e-cigarette users in high risk group.** E-cigarette users will be mainly current or past tobacco smokers, and for that reason are at increased risk of heart attack, stroke or lung cancer. Tobacco cigarette smokers have two to three times the annual death rate of non-smokers, and have ten times the risk of sudden cardiac death. Deaths of those taking up e-cigarette use may be wrongly blamed on the e-cigarette.

**3.4 Dual use.** Smokers may take some time to switch completely from tobacco to nicotine smoking. As long as they continue to smoke even a few cigarettes a day their risk of dying early remains excessive. (The risk of smoking even 1-4 cigarettes a day carries a 60% excess risk of dying early. Smoking 5-9 cigarettes a day doubles the risk of dying early, compared with never smoking<sup>2</sup>). In particular their excess risk of heart attack will not diminish substantially until they quit tobacco smoking entirely.

## 4. Nicotine dose, consumption, and labelling

**4.1 Correct dose.** Each smoker is accustomed to a certain amount of nicotine each day. This varies greatly between smokers, but for each smoker, varies little from day to day. Heavy tobacco cigarette smokers in the United States smoking an average 36 cigarettes (range 20-62) per day absorb about 37 mg per day (range 10-79 mg)<sup>10</sup>.

The e-cigarette can supply 16 mg nicotine per day. Non-inhalers and smokers of light cigarettes inhale less nicotine. If smoking one cartridge of the 16 mg e-cigarette per day is not able to control cravings, a second e-cartridge for the day might be needed.

**Table 1. Nicotine content and delivery or absorption per puff, per smoke, and per day, factory-made tobacco cigarette and Ruyan® e-cigarette compared.**

	Content Nicotine in each unburnt tobacco cigarette, or in each e-Cigarette cartridge** mg	Per puff Nicotine delivery per puff; 99% absorbed## Mg	Per smoke Nicotine delivery and absorption# per cigarette or e-cigarette smoke' mg	Per day* Nicotine delivery and absorption (per 300 puffs from 20 cigarettes or 20 e-cigarette 'smokes' mg
	A	B**	C	D
Factory-made cigarettes	A	B=C/15	C	D=C*20
Regular filter cigarettes	13	0.16	1.4 to 2.4 assume 2.0	28 – 48, assume 38
Ruyan® e-Cigarettes	A	B=A/300***	C=b*15	D=C*20
Ruyan® cartridge Label:16 mg	14~ - 16	0.053	0.80	14-16
Ruyan® cartridge Label = 11 mg	10~ - 11	0.037	0.56	10-11
Ruyan® cartridge Label 6 mg	6~	0.02	0.3	6
Ruyan® cartridge Label 0 mg	0-0.5~	0	0	0-0.5

\* Ruyan® cartridge lasts one to four days. If it lasts four days, divide Ruyan values in D by 4.

\*\* Assumes 15 puffs per cigarette

\*\*\* Assumes 300 puffs per e-cigarette cartridge. Smokers taking larger puffs may finish the cartridge before 300 puffs.

<sup>10</sup> Benowitz ibid. p.6.

# Nicotine absorbed per cigarette = 1.4 mg (Fagerstrom, for Sweden),<sup>11</sup> 2.4 mg (Djordjevic for USA).<sup>12</sup> The nicotine absorbed from tobacco smoking is much greater than what is printed on cigarette packets.

## When nicotine aerosol is inhaled into lungs, approximately 99% of nicotine is retained.<sup>13</sup>

~ ESR Porirua October 2007.

Table 1 shows that, the 16 mg nicotine e-cigarette cartridge provides nicotine equal to 7 to 10 factory-made tobacco cigarettes. Once the smoker stops smoking tobacco cigarettes, the e-cigarette by itself is unlikely to cause nicotine overdose. Any smoker becoming light headed while smoking an e-cigarette, should stop smoking tobacco.

**4.2 Nicotine consumption per day.** As puffs from the 16 mg nicotine cartridge contain one third to one half the nicotine in a tobacco cigarette puff, and e-cigarette smokers take up to four days to finish a cartridge, smokers are most unlikely to absorb more nicotine from e-cigarettes than previously absorbed from tobacco.

Smokers of the e-cigarette say a cartridge lasts 1 to 4 days, which for a 16 mg cartridge is equal to 4 to 16 mg per day daily or equal to 2.5 to 10 tobacco cigarettes a day unaccompanied by tar or gas toxicants (Table 1). Pure nicotine in this dose is neither excessive nor harmful.

As virtually all cartridge nicotine is eventually inhaled, and over 98% of inhaled nicotine is absorbed<sup>13</sup> the consumption of nicotine cartridges per smoker will reliably establish the level of nicotine absorption per day, provided no tobacco or other nicotine product is being used.

**4.3 Accuracy of nicotine dose labels** The only biologically active ingredient of the e-cigarette is nicotine. On analysis<sup>14</sup>, the cartridges labelled as 16 mg actually contained 14.1 mg of nicotine; those labelled 11 mg contained 10.0 mg; those labelled 6 mg contained 5.9 mg; and those labelled 0 mg of nicotine contained 0.5 mg. These data are included in Table 1.

## 5. Risk of addiction

### 5.1 Tobacco versus nicotine addiction.

Generally addiction to nicotine products is much less than to tobacco products.  
The addictive potential of the Ruyan® e-cigarette is uncertain.  
Further research is required.

<sup>11</sup> Fagerstrom K. The nicotine market: An attempt to estimate the nicotine intake from various sources and the total nicotine consumption in some countries. *Nicotine & Tobacco Research*. 2005; 7: 1-8.

<sup>12</sup> Djordjevic MV, Stellman SD, Zang E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *JNCI* 2000; 92: 106-11.

<sup>13</sup> Feng S, Plunkett SE, Lam K et al. A new method for estimating the retention of selected smoke constituents in the respiratory tract of smokers during cigarette smoking. *Inhal Toxicol* 2007; 19: 169-79.

<sup>14</sup> Dickson S. Analysis of e-cigarette cartridges for nicotine content. Environmental Science Research, Porirua. 17 September 2007.

**Other active substances in tobacco.** MAO inhibitor compounds (such as harman and norharman) in tobacco smoke tend to potentiate the effect of the nicotine. If this proves to be a strong factor, then the nicotine-only e-cigarette will be much less addictive than smoking tobacco cigarettes. Even if some become addicted to nicotine through the e-cigarette, this does not increase their risk of cancer, heart or lung disease, or of early death.

**Other factors.** The cost of buying the e-cigarette (currently US 208 dollars), and the need to use a credit card to order it by mail, should deter most young people obtaining the e-cigarette for personal use. If some youths do use it, and develop a taste for nicotine, the price of nicotine refills versus cigarettes will be decisive for many. It also depends on fashion, safety concerns, and whether parents, health groups and doctors approve its use.

## 5.2 Addiction in smokers

The e-cigarette does not cause nicotine addiction in smokers, as most cigarette smokers are already addicted to nicotine. E-cigarettes will not increase the need for nicotine in smokers, as each smoker needs a certain amount of nicotine each day, and the brain receptor cells cannot distinguish where the nicotine molecule comes from (smoked tobacco, tobacco snuff, or e-cigarette). The e-cigarette does not increase the daily customary dose; from the first day of using the e-cigarette most smokers tend to smoke very few tobacco cigarettes.

Once the daily dose is obtained, the smoker will not reach for another puff from either their tobacco cigarette or their e-cigarette: no pleasure is obtained and there is no craving to relieve.

Further research on quitters is required to find out how many will prefer to continue using the e-cigarette one year after quitting smoking.

Smokers quitting smoking in countries which encourage quitting, are likely to use the e-cigarette to gain control of their nicotine needs, and use it temporarily – for a few weeks only, after stopping smoking. Quitting smoking is often part of a lifestyle change which will often include quitting tobacco and nicotine altogether. By the time smokers are ready to quit cigarettes, many are also wanting to be rid of their nicotine addiction.

**The 16 mg, 11 mg nicotine cartridges** are expected to satisfy the cravings and maintain the addiction of smokers who wish to stay on nicotine. This is the subject of further tests in 2008.

On the basis of similarity to the rapid action of nicotine nasal spray, we assume that one year after smokers' first using the e-cigarette as a stop smoking aid, no less than 15% would become long term users of the e-cigarette (as for nicotine nasal spray below)..

**The 6 mg nicotine cartridge** if used up in one day may provide just enough nicotine to maintain addiction. Used over 4 days it would not be sufficient. Very recent quitters

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using the 6 mg cartridge would likely have cravings for cigarettes and be at risk of smoking tobacco again.

**The 0 mg nicotine-labelled cartridge** will not maintain addiction. It will provide 0.002 mg nicotine per puff, 0.025 mg per smoke, which at even 300 puffs a day amounts at most to 0.6 mg per day, much less than the estimated 5 mg daily required to sustain addiction<sup>15</sup>. The labels were therefore safe estimates of the dose of nicotine to be expected, and the 0 mg e-cigarette can be used without risk of creating or maintaining dependence on nicotine. Nicotine is not recommended for non-smokers but for smokers already addicted (dependent) to nicotine, who wish to avoid inhaling tobacco smoke.

**Tobacco cigarettes** Some 84% view their own use of cigarettes as an addiction<sup>16</sup>.

**Comparison with nicotine medications** (Nicotine Replacement Therapy, NRT) Of users of nicotine medications some are still using the medication after one year and assumed to be addicted. (2% for patch, 8% for spray, 9% for gum and 15% for nasal spray)<sup>17</sup>.

## 6. Addiction in young people.

Tobacco, snuff and the e-cigarette can all be expected to induce nicotine addiction in many young people. This involves a subtle loss of autonomy or control over their new habit. Once addicted to nicotine, the concern is that tobacco, snuff and the e-cigarette could be used interchangeably.

The answers to this concern depend on what policies society has put in place to steer young people away from addiction of any kind, and away from tobacco smoking in particular. In 2007, New Zealand smokers could buy an e-cigarette from the internet for the price of a carton of cigarettes. If cigarettes cost much more, more would buy the e-cigarette. Similarly, graphic health warnings on cigarette packets may persuade smokers to quit or switch to the safer e-cigarette.

Addiction to smoking tobacco cigarettes ensures young smokers remain smokers into adult life and continue to smoke beyond 35 years of age when the risks of smoking deaths begin to increase. Similarly smoking the e-cigarette makes it less likely that the smoker will ever want to smoke tobacco cigarettes again.

Young people can use the e-cigarette, as a temporary crutch while stopping smoking and so avoid the future increased mortality risks of smoking. If the e-cigarette was widely available to young people, their cigarette smoking would decrease, life expectancy increase and respiratory health would improve, without any extra mortality from nicotine.

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<sup>15</sup> Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. *New Engl. J Med* 1994; 331:123-125.

<sup>16</sup> National Research Bureau Ltd. *Environmental Tobacco Smoke Study*. 1996. Wellington: Ministry of Health.

<sup>17</sup> Hajek P, McRobbie H, Gillison F. Dependence potential of nicotine replacement treatments: effects of product type, patient characteristics, and cost to user. *Prev Med* 2007; 44: 230-4. Epub 2007 Jan 4.

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### The fate of users of the e-cigarette

Smokers who try the e-cigarette will either:

- Try the e-cigarette experimentally, then revert to tobacco smoking as before.
- Use the e-cigarette as a temporary aid to quitting smoking entirely.
- Switch permanently to e-cigarette (and no longer smoke tobacco) .
- Continue to use both e-cigarette and tobacco cigarettes (See 3.4 above).

The first tobacco cigarettes smoked result in one on four adolescents losing some autonomy (control) over their smoking<sup>18</sup>. Whether some adolescents would soon lose partial control over their use of the pure nicotine e-cigarette is not clear. The e-cigarette is not likely to cause addiction any more than cigarettes, which most adolescents can obtain with ease. On the other hand, the e-cigarette supplies safe nicotine, without risk of early death due to lung cancer, heart disease, or emphysema. A simple, truthful warning is therefore suggested for the e-cigarette:

The proportion of young people who will prefer the e-cigarette over tobacco, and who use it long term, is unknown. It will vary by country. Graphic and varied health warnings on cigarette packets will favour use of the e-cigarette. Better information about the health risks of smoking, and higher prices for tobacco, will mean that as the e-cigarette becomes available, the proportion of young people smoking tobacco should decrease more rapidly.

#### Health warning

Tobacco cigarettes in many countries now warn the smoker “Smoking is addictive”. Similar warnings are needed on the e-cigarette packaging, pointing up the difference between the e-cigarette and tobacco cigarettes.

Although the manufacturer’s pamphlet warns that the e-cigarette is not suitable for young people or non-smoking adults, some may gain access to it.

**“This nicotine product is addictive but avoids the other risks of smoking”.**

If young people see strong health warnings and high prices on tobacco packets, young people will abstain from tobacco smoking and possibly take up e-cigarette smoking instead. In due course, fewer will die early from tobacco smoking.

#### Conclusion.

The invention of the e-cigarette means that society must now distinguish between

- harmful (tobacco) smoking, and harmless (e-cigarette) smoking; and between
- harmful addiction (associated with smoking) and harmless addiction (associated with the e-cigarette).

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<sup>18</sup> DiFranza J, Scragg R, Laugesen M, Wellman R. ‘Diminished Autonomy over Tobacco Can Appear With the First Cigarettes. Addictive Behaviours 2008. doi 10.1016/j.addbeh.2007.12.002.

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Regulators in Western countries are likely to

- prohibit sale of nicotine e-cigarette refills to under-18s, in line with restrictions on cigarette sales to youth
- permit e-cigarette use in most areas where tobacco cigarette smoking is banned
- permit e-cigarette advertising in many countries.
- continue to enforce existing bans on the advertising of smoking tobacco.

## 7. Risk of accidental ingestion of nicotine

Accidental ingestion of the e-cigarette is theoretically possible, though it has not been mentioned in the English news media in their articles on the Ruyan® e-cigarette from China, where 300,000 units are sold annually since 2004. Poisoning by ingesting tobacco cigarettes is rare, even though children can easily access tobacco cigarettes in the home.

**7.1 Ruyan® nicotine cartridges, when sold separately** are packed in individually sealed child-proof canisters. Without scissors, even adults find them difficult to open. In this packaging, unattended children in car or home are not at risk from the nicotine.

**7.2 The nicotine cartridge assembled** into the e-cigarette is better child-proofed than a packet of tobacco cigarettes.

- Many Ruyan® smokers keep their e-cigarette close by, reducing risk of child access.
- Once assembled, the join between the e-cigarette mouthpiece/ cartridge, and the metal shell of the middle section is normally difficult even for an adult to pull apart. It is not a screw join.
- If, unusually, this join was loose, it prevents normal use of the e-cigarette, so does not remain loose for long.
- If unusually a child gained access to it and pulled it apart, put the cartridge in the mouth and sucked on it, then the nicotine impregnated in the cartridge could be absorbed through contact with mouth mucosa causing acute toxicity.
- Swallowing is less likely, as the mouthpiece-cartridge measures 5 cm in length by 1cm diameter, and is rigid and indivisible.

The highest dose e-cigarette cartridge contains 16 mg of nicotine. The factory-made tobacco cigarette contains 13 mg<sup>19</sup>. The lethal nicotine dose for a child is known to be 10 mg.

## 8. Safety of the cartridge liquid and inhaled aerosol

Propylene glycol makes up 89-90% of the liquid in the nicotine cartridge that generates the aerosol inhaled by the e-cigarette smoke. (See Appendix 1, Table 2).

Propylene glycol is virtually non-toxic, See Appendix 3.

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<sup>19</sup> Blakely T, Laugesen M, Symons R. NZ cigarettes have a high nicotine content. NZ Public Health Report 1997; 4: 33-34, and update, 1997;4:85

## 8.1 No tobacco content; nitrosamines extremely low

From November 2007, cartridges do not contain tobacco extract as flavouring agent. (Appendix 1)

**8.1.1 Tobacco-specific nitrosamines** Traces of nitrosamines are found in the e-cigarette cartridge, at a level equal to that found in medicinal Nicorette gum.

The maximum level of tobacco specific nitrosamines of 8 ng TSNA's per gram of cartridge liquid (8 parts per billion or ppb) found in 16 mg nicotine cartridges, compares closely to the 8 ng per gram found in Nicorette gum sold as a nicotine replacement therapy medicine in the United Kingdom<sup>20</sup>. The e-cigarette TSNA content is 200 times less than the amount found in Swedish moist snuff ( 1000 to 2400 ppb), and 150 times less than the amount found in unburnt tobacco in the most popular filter cigarette and cigarette tobacco brands (1230 ppb)<sup>21</sup>.

**Table 2. Tobacco specific nitrosamines in the cartridge liquid of the Ruyan® e-cigarette, November 2007**

Nicotine per Cartridge	Sample ID	NNN (ng/cartridge) Observation	NAT (ng/cartridge) Observation	NAB (ng/cartridge) Observation	NNK (ng/cartridge) Observation	TSNA's
						Ng/cartridge total
0 mg	073277	BDL	BDL	NQ	0.260	0.260
6 mg	073278	1.42	1.02	BDL	0.628	3.068
11 mg	073279	1.83	1.36	NQ	1.01	4.200
16 mg	073280	3.87	2.16	0.693	1.46	8.183
Labstat 2007 <sup>22</sup> .					Average TSNA	3.928
BDL = Below the limit of detection. NQ = Not quantifiable. TSNA = tobacco specific nitrosamines NNN= nitrosanornicotine, NAT= nitrosoanatabine NAB= nitrosoanabasine, NNK= 4-nitrosomethylamino-1-(3-pyridyl)-1-butanone						

**8.1.2 Monoamine oxidase.** The cartridge liquid no longer uses tobacco extract (Appendix 1). Monoamine oxidase (MAO) enzyme in blood platelets is strongly inhibited by tobacco smoke extract but the cartridge liquid had no such effect<sup>23</sup>. MAO has been regarded as a potentiator of the reinforcing (addictive) effects of nicotine, but in the case of the e-cigarette, any nicotine effect would appear to be due to nicotine alone.

## 8.2 No gases of combustion.

There is no flame or fire; and the very high temperatures of a burning cigarette (combustion) are not achieved. Thus we did not detect carbon monoxide on the exhaled breath after e-cigarette use. Similarly, we have not tested and would not expect to find

<sup>20</sup> Stepanov I, Jensen J, Hatsukami D, Hecht SS. Tobacco-specific nitrosamines in new tobacco products. *Nicotine Tobacco Research* 2006; 8: 309-313.

<sup>21</sup> Wahlberg I. Tobacco-specific nitrosamines in unburnt New Zealand tobaccos. Report to Health New Zealand Ltd. Swedish Match 2004. [www.smokeless.org.nz/snuffregulations.htm](http://www.smokeless.org.nz/snuffregulations.htm) at Table 2.

<sup>22</sup> Rickert W. Determination of Tobacco specific Nitrosamines by LC-MS/MS. Project NZ9. Nov.30, 2007. Labstat International ULC. Kingston Ontario, Canada.

<sup>23</sup> Truman P. MAO inhibition of the Ruyan cartridge liquid. Preliminary report. ESR October 2007.

compounds in the cartridge liquid or vapour such as cigarette or diesel smoke toxicants and combustion products such as butadiene, and benzene, and carbon monoxide.

The cartridge liquid was tested for benzo(alpha)pyrene, a probable human carcinogen (detectable in cigarette smoke at 35 nanograms (ng) per cigarette). The value obtained from the e-cigarette liquid was below the method's limit of detection of 1ng<sup>24</sup>. As the e-cigarette cartridge is equivalent in nicotine to no more than 10 cigarettes, e-cigarette smoking delivers 350 times less benzo(alpha)pyrene than does tobacco cigarette smoking.

### 8.3 Impurities

**8.3.1 In Propylene glycol.** Impurities might arise in the manufacture or storage of propylene glycol. On examination of the cartridge liquid, propylene oxide and ethylene oxide (a carcinogen) were not detected (limit of detection 16.75 ug/ml and 42.5 ug/ml respectively<sup>25</sup>. The test however, detected some interference (matrix effect) with the result; the true result may be less or more than these limits of detection. Ethylene oxide has been found in cigarette smoke at 7 ug per cigarette,<sup>26</sup> that is 1000 times the level found here in the e-cigarette<sup>27</sup>.

**8.3.2 Heavy metal traces.** Heavy metals such as chromium, arsenic, and nickel can cause cancer, and lead is a neuro-toxicant. The liquid was tested for heavy metals (Arsenic, Antimony, Cadmium, Chromium, Cobalt, Copper, Lead, Manganese and Nickel), and the concentrations in each case were less than 1 part per million. No hazardous effects are expected from heavy metals at this concentration<sup>2</sup>.

## 9. Risk of cross-infection from use

**9.1 Risk of contamination from the mouthpiece.** Public health agencies typically advise smokers not to share drinking glasses or cigarettes, due to the risk of cross-infection<sup>25</sup> from lip saliva on the mouth end, with the risk of meningitis. This advice holds true for the e-cigarette.

**9.2 Risk of micro-organisms in the cartridge liquid.** Another risk would be if the liquid in the cartridge acted as a culture medium for micro-organisms. The 5% alcohol content of the cartridge liquid (See Appendix 1) might be expected to inhibit growth of micro-organisms.

Environmental Science Research tested one used and one unused Ruyan® cartridge for the presence of the three main classes of micro-organism (aerobic, anaerobic and Legionella)<sup>28</sup>. None was found.

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<sup>24</sup> Northcott GL. Benzopyrene in Ruyan e-cigarettes. Hort Research, Hamilton, NZ. 19 November 2007.

<sup>25</sup> Fitzmaurice P. Testing of Ruyan E-cigarette cartridges for ethylene oxide and propylene oxide content. 18 December 2007. Environmental Science Research. Porirua, Wellington region, New Zealand..

<sup>26</sup> BAT Memo Smith G to Baker RR, 12 January 1988. Reported level of ethylene oxide in cigarette smoke. Available online. URL: [www.library.ucsf.edu/tobacco/batco/GIF/10200/10216\\_0000.gif](http://www.library.ucsf.edu/tobacco/batco/GIF/10200/10216_0000.gif) Bates no. 400987183. Accessed December 2007.

<sup>27</sup> Assuming at least 10 tobacco cigarettes per day, and a maximum one e-cartridge used per day, then the tobacco cigarette smoker would inhale 70 ug ethylene oxide per day, while the e-cigarette smoker would inhale 42.5 ng (0.04 ug) per day at the limit of detection found, or 1750 times less. Allowing for unclear laboratory results, exposure for the e-cigarette smoker is likely to be of the order of 1000 times less.

<sup>28</sup> Analytical Report no.07/15857. ESR Kenepuru Science Centre, Porirua NZ. 6 September 2007.

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We conclude there is no inherent tendency in the design of the e-cigarette towards contamination from growth of organisms in the cartridge liquid. Nevertheless, instructions to users (and to tobacco cigarette smokers) should discourage cigarette sharing because of the risk of transfer of meningococcal meningitis, tuberculosis and other infectious diseases.

### **10. Safety of e-cigarette ‘smoke’ for bystanders.**

Because inhaled nicotine is over 98% absorbed<sup>6</sup>, the exhaled ‘smoke’ is propylene glycol minus the nicotine, and any exhaled PG mist dissipates within seconds. Without the gaseous products of combustion, the ‘smoke’ is not harmful to bystanders. The ‘smoke’ or mist is not tobacco smoke, and not from combustion – no flame is lit – and is not defined as environmental tobacco smoke. and e-cigarette “smoking” would be permitted under New Zealand’s Smoke free Environments Act<sup>29</sup>.

### **11. Further safety testing**

Analyses have been requisitioned for further testing for possible impurities in the cartridge liquid.

In January to March 2008, as part of a further trial for the efficacy, Clinical Trials Research Unit, University of Auckland will independently monitor use of the e-cigarette by some 50 subjects, over the course of one day, and record any adverse effects.

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<sup>29</sup> Johnston M. No smoke, no fire, just nicotine. NZ Herald 8 December 2007, quoting Dr Ashley Bloomfield, Chief Advisor, Public Health, New Zealand Ministry of Health.

## Appendix 1. Safety of the cartridge liquid in the Ruyan e-cigarette

### Summary:

Based on the manufacturer's information, the composition of the cartridge liquid is not hazardous to health, if used as intended.

**Table 1: Chemical compositions (quantity) released from each cartridge**

Chemical content released from each cartridge	Cartridge Specification, named by nicotine content			
	16mg	11mg	6mg	0mg
Water (mg)	40	40	40	40
Alcohol (mg)	50	50	50	50
Propylene glycerol (mg)	888	893	898	904
Nicotine (mg)	16	11	6	0
Flavor Base (mg) *	6	6	6	6
Total (mg)	1000	1000	1000	1000

Source: Manufacturer's data

**Table 2: Chemical compositions (percentage w/w) released from each cartridge**

Chemical content released from each cartridge	Cartridge Specification, named by nicotine content.			
	16mg	11mg	6mg	0mg
Water	4%	4%	4%	4%
Alcohol	5%	5%	5%	5%
Propylene glycerol***	88.8%	89.3%	89.8%	90.4%
Nicotine	1.6%	1.1%	0.6%	0.0%
Flavour base *	0.6%	0.6%	0.6%	0.6%
Total	100%	100%	100%	100%

Source: Table 1.

\*\*\* See Appendix 3. Safety of Propylene Glycol.

### \*Safety Evaluation: 4-hydroxy-2,5-dimethyl-3(2H)-furanone and Acetyl pyrazine

#### 1). 4-hydroxy-2,5-dimethyl-3(2H)-furanone

4-Hydroxy-2,5-dimethyl-3(2H)-furanone (FEMA 3174, CoE 536) is naturally occurring in various foods and plays an important role in the flavor of numerous fruits as well as in roasted products. 4-hydroxy-2,5-dimethyl-3(2H)-furanone has the odor and taste of fruity, caramelized pineapple-strawberry and is widely used in fresh bread, butter, chocolate, chocolate cocoa, coffee, meat roasted and nut almond.

Over 90% of annual production volume of tetrahydrofuran and furanone flavoring agents is 4-hydroxy-2,5-dimethyl-3(2H)-furanone. The estimated daily *per capita* intake is 5300 µg in Europe and 5200µg in the USA. Due to the large consumption, the safety of 4-hydroxy-2,5-dimethyl-3(2H)-furanone is extensively investigated. The oral LD<sub>50</sub> for

mouse is 1,608mg/kg. Genotoxicity is observed at high dose, but it is related to a mechanism involving reactive oxygen species, rather than the generation of an active metabolite. A 2-year study in which rat were given a dose up to 400mg/kg bw from diet daily showed no evidence of carcinogenicity. Considering the fact that NOEL of 200mg/kg bw in rat is >2300 times the daily intake as a flavoring agent, the WHO Committee on Food Additives concludes that “the safety of this agent would not be a concern at the estimated current intake”<sup>1</sup>.

## 2). Acetyl pyrazine

Acetyl pyrazine (2-acetyl pyrazine, FEMA 3126, CoE 2286) is found in beef, coffee, popcorn, sesame seed, almond, wheat bread, cocoa, peanut, pork and potato chips, etc. According to the documentation from tobacco industry, acetyl pyrazine is added to cigarettes to give a pop-corn-like flavor and aroma to the tobacco.

Acetyl pyrazine belongs to a group of 41 flavoring agents consisting of pyrazine and pyrazine derivatives. Among them, acetyl pyrazine is detected naturally and its daily intake threshold for human is 540mg/day. The estimated annual consumption of acetyl pyrazine is 920kg in the USA, corresponding to 120µg/person per day. In Europe, the intake of acetyl pyrazine is 14µg/person per day. The consumption of the parent substance pyrazine from food is about 36,000 times greater than its intake as a flavoring agent<sup>2</sup>. Compared to the 540mg/day human intake threshold, the amount is much lower and it is not a safety concern<sup>3</sup>.

Toxicity data support the above conclusion. In an acute toxicity test on rat, LD<sub>50</sub> through gavage was >3,000mg/kg. A group of 32 Wistar rats were maintained on diets containing acetyl pyrazine 8.2mg/kg bw for 90 days. Control group was given basic diet. At the end of experiment, measurements of growth rate, food intake, haematological and clinical chemical parameters, organ weights, and gross and histopathological appearance showed no differences between test and control animals<sup>4</sup>.

**Conclusion.** Based on the manufacturer’s information, the composition of the cartridge liquid is not hazardous to health, if used as intended.

## References

1. WHO Technical Report Series 928: Evaluation of Certain Food Additives, Geneva, 8-17 June 2004.
2. Stofberg, J. & Kirschman, J.C. (1985) The consumption ratio of flavouring materials: A mechanism for setting priorities for safety evaluations. *Food Chem. Toxicol.*, **23**, 857–860.
3. WHO food additives series 48: Safety Evaluation of certain additives and contaminants-pyrazine derivatives.
4. Posternak, J.M., Dufour, J.J., Rogg, C. & Vodoz, C.A. (1975) Summaries of toxicological data: Toxicological tests on flavouring matters. II. Pyrazines and other compounds. *Food Cosmet. Toxicol.*, **13**, 487–490.

**Appendix 2. Ruyan e-cigarette. New Zealand testing to date, as of 18 December 2007.**

Topic	Name of test	Purpose	Status	Result
<b>Toxicology</b>	Nicotine content of liquid in cartridges	Confirm labelling states contents correctly	Completed	Generally around 90% of content stated
	Benzo-alpha-pyrene in liquid	Whether liquid carcinogenic	Completed	None found
	Heavy metal traces in cartridge liquid	Whether liquid carcinogenic	Completed	Less than one part per million
	Tobacco specific nitrosamines in cartridge liquid	Whether liquid carcinogenic	Completed	Same as in Nicorette gum
	Ethylene and propylene oxide	Test for carcinogenic impurities	Completed	Not detectable. See text.
	Test for bacteria	To rule out infectivity. Whether bacteria grow in used and unused cartridges.	Completed	No growth of aerobic, anaerobic bacteria or legionella
	<b>Adverse effects</b>	50 smokers to use each product for one day	Note how adverse events compare.	February-March 2008
<b>Satisfaction ratings</b>	50 smokers to use 16 mg e-cigarette for one day; and on other days use 0 mg e-cigarette, 10 mg Nicorette inhaler and their own cigarette.	Rate satisfaction with product at end of day.	February-March 2008	
<b>Efficacy</b> Effect on urge to smoke (cigarette cravings)		Compare urge to smoke before are many times after using each product.	February-March 2008	
<b>Efficacy</b> Pharmaco-kinetic study	Blood nicotine taken before and after using the e-cigarette. (12 tobacco smokers)	Test and compare increase in blood nicotine after use of each product over two hours.	February-March 2008	

### **Appendix 3. Safety of Propylene Glycol**

**Summary:** Propylene glycol is virtually non-toxic.

**Properties and uses.** Propylene glycol C<sub>3</sub>H<sub>8</sub>O<sub>2</sub> (PG) is a completely water soluble liquid, and is prepared by hydrolysis of propylene oxide under pressure at high temperature without a catalyst. It is used in pharmaceuticals, as a drug vehicle (for example as an FDA approved solvent for intravenous diazepam) and preservative. It is used also in personal lubricants. It is used in semi-moist pet food and as a humectant for tobacco. In the food industry it is used as a solvent, humectant and preservative. Its mist is used in theatrical stage productions.<sup>1</sup>

#### **Animal studies**

In a study of rats exposed for 60 hours over two weeks, the highest concentration tested, 1800 mg/m<sup>3</sup>, which was the highest concentration that could practically be generated, was the no-observed-effect level (NOEL). PG does not appear to pose a significant hazard via inhalation of either the vapor or a vapor/aerosol mixture.<sup>2</sup>

Addition of propylene glycol at 2.2% w/w tobacco does not increase the toxicity of cigarette tobacco.<sup>3</sup> In rats PG levels in plasma and lung are super-imposable with half an hour. A mild cumulative build up (30% or less) occurred after 28 days.<sup>4</sup>

#### **Propylene glycol in humans**

The toxicology website <http://toxnet.nlm.nih.gov/> was searched for PG, using terms such as human, aerosol, NOEL, carcinogenicity, inhalation.

A review of PG has concluded it is safe for use in cosmetics at concentrations up to 50%.<sup>5</sup>

**Absorption** PG vapour has 100% deposition efficiency in human airways.<sup>6</sup>

It is partly absorbed on inhalation. PG is absorbed completely from the gastrointestinal tract and partly via the skin and the lungs.

**Metabolism.** It is metabolized to lactic acid and pyruvic acid, and further oxidized to glycogen or carbon dioxide and water. In man, approximately 20 - 25% of the PG is eliminated unchanged via the kidney.

**Toxicity** The website [www.pneumotox.com](http://www.pneumotox.com) devoted to inhalational toxicology, registers one case report of bronchospasm<sup>7</sup> but no other adverse effects.

Since PG is less efficiently absorbed following dermal and inhalation exposure compared to oral exposure, it is likely to have a low acute toxicity by these routes of exposure. CNS depression causing mortality has been described in premature infants after repeated exposure to medication containing PG.<sup>8</sup>

**Carcinogenicity.** There is no evidence that PG is a carcinogen.

**PG exposure per puff of the e-cigarette** The cartridge of the e-cigarette contains approximately 1g of PG, of which 0.9 g is extractable from the pad. The concentration of PG in the mouth from one drag of the e-cigarette (900 mg per cartridge, 300 puffs = 3mg) is 3 mg per mouthful).

**PG exposure per day of using e-cigarette** If the cartridge lasts 2-3 days as expected, then the inhaled dose is 0.3 to 0.45 g per day, and if used more intensively, could result in 0.9 g of PG inhaled and probably absorbed.

**Absorption** PG is absorbed rapidly and completely when taken orally. Humans have been given 40 g per 12 hours for 3 days to establish a steady state. After 3 days blood levels reached maximum one hour after administration of the PG dose.<sup>1</sup> We could find no data on the proportion of PG absorbed by inhalation. However the proportion is expected to be high, as it is highly soluble.

**No-observed-effects level (NOEL) and RfD (reference dose)** for humans for sub-chronic (less than a lifetime) and chronic inhalational exposure to PG is estimated by US EPA at 116 mg per 70 Kg human. This level, derived from rat studies, allows a safety factor of 100, 10 for inter-species extrapolation, and 10 to allow for susceptible individuals.<sup>1</sup> This NOEL, however, is artificially low - an artefact of the vapour pressure, as the researchers could not ensure higher concentrations of PG into the air breathed by the rats.

**Inhalational Minimal Risk Levels** No MRLs for acute- or chronic-duration inhalation exposure to propylene glycol were derived because data are insufficient.<sup>9</sup>

**Inhalation threshold.** The USEPA has developed no inhalation threshold value for it, nor has Cal/EPA. Inhalation toxicity is not an issue.

<sup>1</sup> Office of Health and Environmental Assessment. EPA. Health and Environmental effects document for propylene glycol. ECAO-CIN-GO26. Prepared for Office of Solid Waste and emergency response. EPA 1987.

<sup>2</sup> Suber et al., Subchronic nose-only inhalation study of propylene glycol in Sprague-Dawley rats. Food Chem Toxicol 1989; 27:573-583.

<sup>3</sup> Heck JD, Gaworski CL, Rajendran N, et al. Toxicological evaluation of humectants added to cigarette tobacco: 13-week smoke inhalation study of glycerin and propylene glycol in Fischer 344 rats. Inhal Toxicol 2002;14: 1135-52.

<sup>4</sup> Venitz J, Werley MS. Systemic and pulmonary pharmacokinetics (PK) of propylene glycol (PG) after inhalation of a condensation aerosol in rats for 28 days. Presented at AAPS annual meeting 2003, Salt Lake City.

[http://www.chrysalis-technologies.com/publications/AAPS\\_Systemic%20and%20Pulmonary%20PK%20of%20PG.pdf](http://www.chrysalis-technologies.com/publications/AAPS_Systemic%20and%20Pulmonary%20PK%20of%20PG.pdf)

<sup>5</sup> Anonymous. Final Report on the Safety Assessment of Propylene Glycol and Polypropylene Glycols J Am College of Toxicology. 1994; 13: 437-491. Final draft.

<sup>6</sup> Soderholm SC, Anderson DA, Utell MJ et al. Method of measuring the total deposition efficiency of volatile aerosols in humans. J. Aerosol Science. 1991; 22: 917-26.

<sup>7</sup> Spreux A, Boyer A, Baldin B, et al. Toux et crise d'asthme declenchees par le propylene glycol. Propylene glycol-induced cough or asthma. A case report. Therapie 1996 ; 51 : 561-562.

<sup>8</sup> Mortenson B. Health effects of selected chemicals. 2. Propylene glycol. Nord 1993; 29: 181-208

<sup>9</sup> ATSDR (Agency for Toxic Substances and Disease Registry.) Toxicological profile for ethylene glycol and propylene glycol. Sept 1997. <http://www.atsdr.cdc.gov/toxprofiles/tp96-c2.pdf> at p.108.