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APPENDIX A6.1.4.7 CARBOXYHEMOGLOBIN (COHb)
HEALTH EFFECTS OF SMOKING CESSATION

Short Term Health Effects

Carboxyhemoglobin (COHb)

Internal Report

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1. BACKGROUND

Carbon monoxide (CO) is produced by the incomplete combustion of organic material, including tobacco. CO binds to hemoglobin (about 200 times more strongly than oxygen) to form carboxyhemoglobin (COHb) and the resulting lowered oxygen binding and transport means that less oxygen is available at peripheral tissue sites and leads to hypoxia. COHb may be considered a biomarker of exposure and biological effect, the latter because the saturation of hemoglobin with CO is a direct measure for the biological effect of CO, namely impairment of the oxygen supply of organs.

Cigarette smoking is known to elevate both respiratory and blood CO levels and, therefore, raise the COHb level. In general, COHb levels in non-smokers are less than 2% [1] whereas conventional cigarette (CC) smokers can have COHb levels of 3-15% (see Table 2) and even non-smokers exposed to environmental tobacco smoke (ETS) have increased COHb (5.0ppm (3.0 to 8.0) for exposed subjects compared to 2.5ppm (1.0 to 4.0) in exhaled breath of 100 subjects in each group. Median (interquartile range)) [2].

Raised COHb levels are associated with increased numbers of cardiac events, including fatal and non-fatal myocardial infarction, and lowering of COHb rapidly leads to an increase in the respiratory indices of vital capacity (VC), forced expiratory flow 25-25 (FEF25-25) and forced expiratory volume in 1 second (FEV1) [3, 4].

CO-induced adverse effects on the cardiovascular system have been shown in a series of controlled human exposure studies of individuals with cardiovascular disease (CVD) [5, 6]. Moreover, studies of chronic environmental exposure to CO are consistent with the results of the controlled human exposure studies. Positive associations between ambient CO exposure and hospital admissions for CVD including ischemic heart disease (angina pectoris) and congestive heart failure have been reported [7].

In a double-blind, randomized, crossover study [8] involving 15 patients with stable angina, breathing CO raised the COHb levels from 1.09% to 2.02% and caused a decrease in the time that exercise could be undertaken before angina pectoris occurred (exercise duration was 324.5±98.5 sec before and 330.3±100.7 sec after breathing compressed air and 321.7±96.0 sec before and 289.2±88 sec after breathing 50ppm CO for 1 hour). It was concluded that a level of 2% COHb aggravated angina pectoris due to coronary artery disease. It has also been shown that elevated COHb levels are related to decrements in exercise duration in healthy subjects and contribute to earlier fatigue in smokers compared with non-smokers who exercise [9].

In smokers and in non-smokers, the levels of COHb correlate with CVD risk [3, 10, 11]. In a population-based cohort study of 1,489 never smokers, 1,685 former smokers, and 2,901 current smokers, aged 28 to 61 years, it was shown that the age-adjusted relative risk (RR) for the incidence of stroke and cardiac events was 1.46 times (95% confidence interval [CI]: 0.98-2.18) higher in moderate and heavy smokers with high COHb levels of >2.9% in comparison to low COHb levels of around 0.86% [11]. In a cohort study involving 2893 never smokers, the risk of cardiovascular events and CVD death increased with increasing COHb levels [3]. The adjusted RRs for cardiac events and CVD death were 3.70 (95% CI: 1.96-7.03) and 3.43 (95% CI: 1.62-7.27), respectively,

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comparing never smokers with COHb levels >0.67% to those with COHb levels below 0.5% [3]. In a study of 2983 never smokers, COHb levels increased the RR for cardiac events and all deaths by up to 2.53 (95% CI:1.28-4.98) [10].

The aim of the present research was to identify published work relating to COHb as a biomarker of carbon monoxide intake related to smoking conventional cigarettes, the effects of smoking and smoking cessation on the levels of the biomarker and its relationship to CVD and respiratory diseases.

2. METHODS

Three searches of the PubMed literature data base were conducted on July 30th 2014 for English language articles within the time frame of 2008 to the present day.

Search 1: To identify literature that linked smoking or nicotine replacement to carboxyhemoglobin using the search string: ((COHb OR carboxyhemoglobin) AND (smokers OR smoking OR nicotine replacement OR cessation) AND ("2008"[Date - Publication]: "2014"[Date - Publication]) AND English[Language].

Search 2: To identify literature reporting an association between carboxyaemoglobin and cardiovascular disease using the search string: (COHb OR carboxyhemoglobin) AND (cardiovascular disease AND association) AND ("2008"[Date - Publication]: "2014"[Date - Publication]) AND English[Language].

Search 3: To identify literature reporting an association between carboxyhemoglobin and respiratory disease using the search string: (COHb OR carboxyhemoglobin) AND (respiratory disease AND association) AND ("2008"[Date - Publication]: "2014"[Date - Publication]) AND English[Language].

Among the identified studies a set of specific criteria was applied to determine which papers should be selected for inclusion within the report.

The following inclusion criteria were applied:

Studies investigating the association of cigarette smoking, smoking cessation or nicotine replacement therapy (NRT) on COHb

Studies investigating the association of COHb with cardiovascular disease or respiratory disease

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The following exclusion criteria were applied:

1. Studies that used the measurement of COHb simply for control purposes (e.g., results were adjusted for differences in COHb between populations, but COHb itself was not an endpoint)
2. Studies involving dietary, pharmacological or exercise interventions in which COHb was an endpoint, but lacking a clear link between COHb and either a disease of relevance or smoking
3. Studies in patients with a disease not covered by the search categories (e.g., cancer, HIV infection, periodontitis) where there was no clear link between COHb and either a disease of relevance or smoking
4. Studies of passive or parental smoking
5. Studies showing a link between COHb and either a disease of relevance or smoking, but in a defined, narrow population (e.g., pregnant women, individuals with a particular haplotype, individuals with a specific disease) or tissue (e.g., retina, gums)
6. Studies reporting results from *In vivo* animal experiments
7. Studies in which COHb was measured for toxicological or forensic purposes
8. Studies with no comparison between smoking and non-smoking/switching/cessation
9. COHb not measured or presented as AUC

3. FINDINGS

Search 1 produced 102 articles, of which 13 were considered for inclusion, searches 2 and 3 produced 3 and 4 articles respectively which were all excluded because the COHb measured lacked any link to disease or smoking (see Table 1.)

The literature searches identified 13 smoking-related studies (smokers vs non-smokers: [12-15]; smokers only: [16, 17]; smokers vs quitter/switchers: [4, 14, 18-24] that met the inclusion and exclusion criteria and the information from these articles was used in the preparation of this document. The reasons for the exclusion of articles from the review are described below in Table 1 which provides an overview of the results from the three searches together with the reasons for exclusion.

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Table 1. Search results and distribution across the exclusion criteria.

	Search 1	Search 2	Search 3
Number of articles retrieved	102	3	4
Articles rejected due to:			
E1. COHb used only as control/biomarker of exposure	17		
E2. COHb lacked link to disease or smoking	16	3	4
E3. Disease not covered by search categories	26		
E4. Studies of passive or parental smoking	6		
E5. Studies in a narrow population (e.g. pregnant women)	3		
E6. Studies using *in vivo* animal models	10		
E7. Studies in which COHb was measured for toxicological or forensic purposes	7		
E8. Studies with no comparison to smoking and cessation/switching	2		
E9. COHb not measured or presented as AUC	2		
Articles selected for review	13	0	0

The 109 articles retrieved by the three searches are listed in Appendix 3 – Appendix 5 with those excluded according to the above selection/exclusion criteria grouped related to their reason for exclusion (E1 – E9).

4. BIOMARKER-DISEASE LINK

4.1. Cardiovascular disease

No literature was identified that provided information on the association between carboxyhemoglobin and cardiovascular disease.

4.2. Respiratory disease

No literature was identified that provided information on the association between carboxyhemoglobin and respiratory disease.

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5. SMOKING-BIOMARKER LINK

A clear link between cigarette smoking and blood carboxyhemoglobin levels has been demonstrated in earlier research and measurement of plasma COHb content is routinely used as a biomarker of exposure to tobacco smoke [1]. It has also been shown that levels of plasma COHb fall rapidly following smoking abstinence, even after periods as short as 12 hours [25]. Table 2 provides an overview of the differences in COHb between smokers and non-smokers taken from historical literature published outside the time frame of the current literature search.

Table 2. Historical data showing average concentrations (%) of COHb in smokers and non-smokers.

Author reference	Smokers	N	Non-smokers	N
Cole (1975) [26]	5.50(2.2-13.0)[a]	100	0.97(0.2-2.5)[a]	120
Szadkowski et al. (1976) [27]	3.37(1.76)[b]	115	0.72(0.25)[b]	37
Saloojee et al. (1982) [28]	7.09(2.9)[b]	360	0.73(0.41)[b]	79
Jarvis et al. (1984) [29]	3.90[e]	94	0.90[e]	46
Pojer et al. (1984) [30]	4.36(2.09)[b]	187	0.93(0.52)[b]	181
Heinemann et al. (1984) [31]	6.90(4.0-10.2)[c]	472	2.20(1.7-2.7)[c]	171
Laranjeira (2000) [2]	5 (3-8) ppm[f]	100	2.5 (1-4)ppm[f]	100

[a] mean and (Range); [b] mean(SD); [c] mean (10 and 90 percentiles); [d] mean(SEM); [e] mean value only provided; [f] median (interquartile range) in exhaled breath

5.1. Smoking

All of the articles in which smokers were compared to non-smokers retrieved from the current literature search showed that smoking increased the blood carboxyhemoglobin levels above those found in non-smokers (Table 3), findings that are in line with previously published data as summarized in Table 2 [12-15]. For the differentiation of smokers and non-smokers, cut-off levels with acceptable sensitivity and specificity were suggested as 1.6-2.0% COHb [1]. In a recent European study on exposure markers for smoking, COHb levels of 0.23 (±0.40 SD)% were found for non-smokers and 3.63 (±2.21 SD)% for smokers [15]. Similar results were observed in a US study [13].

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Table 3. Current literature showing average concentrations (%) of COHb in smokers and non-smokers.

Author reference	Smokers	N	Non-smokers	N
Roethig et al. (2009) [13]	5.26(0.04)[b]	3585	1.45(0.02)[b]	1077
Xavier et al. (2013) [12]	2.02(1.57-3.9)[a]	27	0.45(0-1.2)[a]	24
Ramos et al. (2011) [14]	1.25(0.63-3.0)[a]	33	0.31(0.0.75)[a]	33
Lindner et al. (2011) [15]	3.63 (2.21)[c]	1148	0.23 (0.4)[c]	398

[a] mean(Range); [b] mean(SEM); mean(SD)

5.2. Smoking cessation

In most of the articles that were retrieved and which studied effects on COHb following quitting or switching to a potentially less harmful product, the authors noted a reduction in blood carboxyhemoglobin levels following quitting or switching [4, 14, 19-24, 32]. In only one publication, where users of conventional cigarettes switched to a tobacco heated system, did the authors find no differences in the COHb levels between the two groups [18]. Following smoking cessation, the levels of COHb decline quickly as its half-life is between one and four hours in blood with its elimination being mainly dependent on ventilation rate and physical activity [1]. In one historical study published in 1986, the COHb level decreased from 6.55 ± 0.4% to 1.06 ± 0.16% after 12 hours of cessation [25]. Similar results have been found in more recent studies where smokers switched from conventional cigarettes to electrically heated cigarettes and had COHb levels monitored 8 days after switching as contained in Table 4. [20-23, 32]. Decreases in COHb were also observed after longer periods [4, 18, 19, 24].

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Table 4. Changes in COHb (%) following quitting or switching to Electrically Heated Cigarette smoking system (EHCSS).

Author reference	n	Before quitting	After quitting	Quitting duration
Frost-Pineda et al. (2008) [23]	60	6.6 ± 1.8	2.1 ± 0.9 (switch to EHCSS	8 days
Roethig et al. (2007) [32]	20	6.42[a]	1.3 (switch to EHCSS)[a]	8 days
Ramos et al. (2011) [14]	33	1.52 ± 1.0	0.552 ± 0.30	180 days (n=9)
Tricker et al. (2012) [20]	16	3.54 ± 1.5	0.48 ± 0.23	8 days
Tricker et al. (2012) [21]	16	5.53 ± 1.63	1.17 ± 0.32	8 days
Van Staden et al. (2013) [24]	15	4.37 ± 2.11	2.5 ± 1.23 (switch to e-cig)	14 days
Polonia et al. (2009) [19]	31	5.9 ± 1.67	1.7± 0.56	6 months
Tricker et al. (2012) [22]	32	4.41 ± 1.38	0.45 ± 0.25	8 days
Sakaguchi et al. (2014) [18]	46	6.25(5.51-7.09)[b]	7.03(6.43-7.67)[b] (switch to EHCSS)	28 days
Pezzuto et al. (2013) [4]	181	3.6 ± 1.5	2.1 ± 0.9	3 months

Values are mean±SD except a: only means are graphed, b: mean (Range)

According to these findings smoking cessation, by reducing the levels of carbon monoxide and thus carboxyhemoglobin to near normal levels of around 2% or less, improves the oxygen-carrying capacity of the blood resulting in clinically significant improvements in exercise capacity, especially in subjects with coronary artery disease. These levels would be within the range suggested by The World Health Organisation (WHO) in their established guidelines for indoor air quality to ensure that a COHb level of 2.5% is not exceeded with the intent of protecting populations at risk, such as subjects with latent coronary artery disease, suffering from acute ischemic heart attacks due to the hypoxic effects of increased CO exposure [7].

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6. CONCLUSION

6.1. Role in MRTP assessment

The threshold of 2.5% COHb that has been set by the WHO can be considered useful in the assessment of candidate MRTPs to demonstrate a reduction of risk towards COHb-associated adverse health effects. In-house clinical studies ranging from 5 days up to 3 months in duration have shown that smokers who switched to the PMI Tobacco Heating System (THS) had a substantial reduction of COHb levels. In a study (SPA0401) with THS 1.0 (non-menthol) the COHb levels measured were close to those in smokers fully abstinent from smoking. The reported level of COHb was 5.65±1.80% in the CC study group, 1.36±0.96% in THS 1.0 group, and 0.44±0.25% in smokers abstinent for 8 days [22]. Similar changes in COHb levels (baseline 3.57±0.1.5) were found after 12 weeks of use of THS 1.0 (EHCK6/02/04) under ambulatory conditions, where morning COHb levels after 12 weeks were 5.13±0.54 for subjects who continued smoking who 2.49±1.78 for those who switched to an EHCSS [33].A clinical study conducted in 2012 (Study ZRHX_EX-01) with THS 2.1 showed a 75% reduction in COHb compared to baseline (from 5.8±1.2 to 1.38±0.12%) after 1 week of exclusive, ad libitum use of the product (Figure 1).

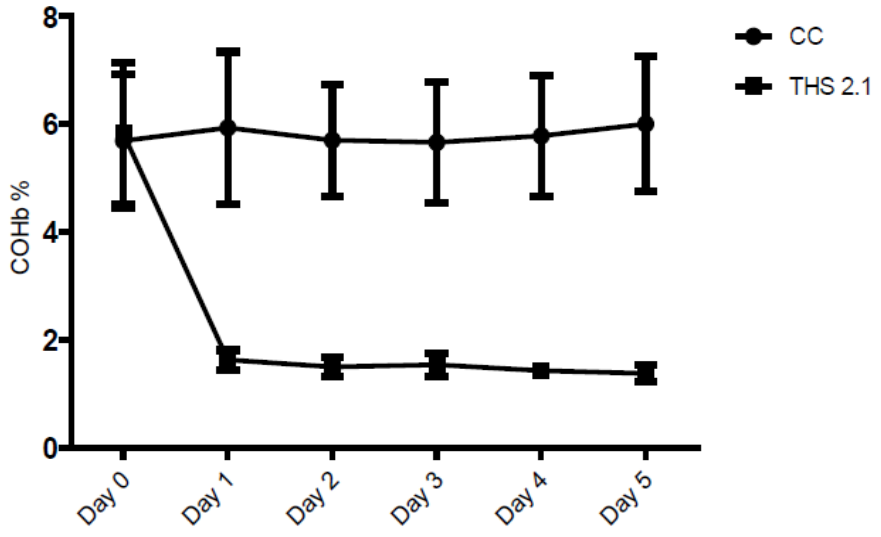


Figure 1. Average carboxyhemoglobin levels over 5 days of ad-libitum use of the THS 2.1 [Study ZRHX_EX-01] [34]a

[a]Carboxyhemoglobin (mean ± SD). At baseline (Day 0) all 40 subjects smoked conventional cigarettes (CC) and were randomly allocated to either continue with CC or switch to the Tobacco Heating System version 2.1 (THS 2.1). Subjects were monitored for COHb during 5 days in confinement [Study ZRHX_EX-01].

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The reduction of COHb levels to below or close to 2% in studies with the THS suggests a substantial favorable change for the smoker at risk of ischemic heart disease.

Table 5 summarizes the strength of the available evidence on COHb for MRTP assessment.

Table 5. Strength of evidence for MRTP assessment.

Definition	Evidence
Biological Plausibility	The role of COHb and related adverse effects caused by hypoxia in organs and tissues with high oxygen consumption such as the brain, the heart and exercising skeletal muscle are well understood and physiologically plausible.
Dose-response	Strong and consistent dose-related association of CO-induced adverse effects on the cardiovascular system.
Benchmark to cessation	Strong and fast smoking cessation effect, with a steep decrease of COHb levels within 24 hours to levels observed in never-smokers.
Consistency [(1)]	Multiple cross-sectional and prospective epidemiologic studies have demonstrated increased levels of COHb to be an important risk factor for acute and chronic cardiovascular, neurological and maternal adverse effects. In subjects with coronary artery disease, elevated levels of COHb contribute to cardiovascular mortality and the early course of myocardial infarction.
Coherence [(2)]	Adverse effects of COHb and their reversibility have been consistently demonstrated in clinical studies.

[(1)] Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect [35]

[(2)] Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, lack of such evidence cannot nullify the epidemiological effect on associations [35]

In summary, although the literature search provided no evidence of a direct link between COHb levels and disease, COHb should be considered as a clinical risk endpoint for the assessment of MRTP since it reflects exposure to carbon monoxide which is associated with respiratory, cardiovascular and inflammatory diseases. Carbon monoxide in blood,

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as assessed by the COHb%, is an accepted indicator of the cardiovascular risk in smokers. The biological, epidemiological and clinical trial information is in line with the induced effects observed upon smoking cessation, suggesting that a decrease in COHb mediates some of the reduced CVD risk observed after quitting smoking.

6.2. Effect size considerations

Data from our studies has shown that switching from conventional cigarette use to a MRTP can lower to levels close to the early morning 1% COHb measured in middle-aged non-smoking men in as little as 8 days [20-22]. The pre- and post-switching COHb values are summarized in Table 6. This reduction in COHb levels is in line with the threshold that has been established by the WHO. Future studies should be powered so that they can confirm this clinically relevant effect.

Table 6. COHb measurements in subjects who switched from CC to EHCSS in in-house studies.

Author reference	Before switching Mean ± SD	8 days post switching Mean ± SD	n
Tricker et al. (2012) [22]	4.57 ± 1.55	1.36 ± 0.96	32
Tricker et al. (2012) [21]	5.04 ± 1.96	2.07± 0.48	28
Tricker et al. (2012) [20]	3.68 ± 1.16	0.93 ± 0.39	28
ZRHX_EX-01	5.80 ± 1.20	1.38 ± 0.12	20

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7. APPENDICES

7.1 Appendix 1 Overview of included studies

7.2 Appendix 2 References related to the included studies

7.3 Appendix 3 Excluded studies from search 1

7.4 Appendix 4 Excluded studies from search 2

7.5 Appendix 5 Excluded studies from search 3

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7.1. Appendix 1 Association between smoking, cessation/switching and COHb

Table A1. Selected studies showing association between smoking, cessation or switching and COHb retrieved in the current search.

Source	Country	Period	Design	Study population	Study size (n), sex, age (mean±sem or range)	Comments
Xavier (2013) [12]	Brazil	2010	Cross sectional	Active smokers & non-smokers	99; M+F; mean age 46-51 years	24 age-matched non-smokers
Mendes (2009)[16]	USA	N/A	Stratified, cross sectional	Smokers	3,625; M+F; mean age 41.7±12.71 years	Smokers in 4 tar categories ≤ 2.9mg; 3-6.9mg; 7-12.9mg; ≥13.0mg
Roethig, 2009 [13]	USA	2002-2003	Stratified, cross-sectional	Adult smokers and non-smokers	4,662, M+F; 21-88 years	21+ years of age, in generally good health from 31 states
Wang, (2010) [17]	USA	2002-2003	Cross-sectional	African-American and white adult smokers	3,341, M+F; 21-80 years	21+ years of age, in generally good health from 31 states. Menthol cf non-menthol
Ramos (2011)[14]	Multi-national	N/A	Smoking cessation program	Smokers	33; M+F; mean age 49±12 years	Smokers who quit over 180 days

(table continues)

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Source	Country	Period	Design	Study population	Study size (n), sex, age (mean±sem or range)	Comments
Polonia (2009) [19]	Portugal	N/A	Smoking cessation program	Smokers	71; M+F; mean age 22-29 years	Smokers who quit over 6 months
Sakaguchi (2014) [18]	Japan		controlled, semi-randomized, open-label, residential study	Healthy Japanese male smokers	70 M; 27.8±6.52 (switchers); 28.7±7.16 (conventional cig)	
Pezzuto (2013) [4]	Italy	Mar-Dec 2009	Smoking cessation program	Smokers	181; M+F; mean(SD) age 53(5)reducers; 55(1.5) quitters (years)	Smokers with ≥15 pack-year history
Tricker (2012) [22]	UK	N/A	Randomized, controlled, parallel-group, open-label	Smokers	175; M+F mean(SD) age 31±8.3 smokers; 27.6±6 quitters (years)	Smokers of 10-25 cigarettes/day
Tricker (2012) [20]	Korea	N/A	Randomized, controlled, parallel-group, open-label	Smokers	99; M+F mean(SD) age 24.1±4.1 smokers; 23.4±3.4 quitters	Smokers of 10-30 cigarettes/day
Tricker (2012) [21]	Japan	N/A	Randomized, controlled, parallel-group, open-label	Smokers	131; M+F; mean(SD) age 23.5±2.2 smokers; 23.9±2.3 quitters	Smokers of 10-30 cigarettes/day

(table continues)

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Source	Country	Period	Design	Study population	Study size (n), sex, age (mean±sem or range)	Comments
Frost-Pineda (2008) [23]	USA		Randomized, controlled, forced-switching, open-label, parallel-group	Smokers	100; M+F; mean(SD) age 31.7(10.3) smokers; 33.8(11.5) switchers; 30.7(8.6) quitters	Smokers of 10-30 cigarettes/day
Van Staden (2013) [24]	S. Africa		Single group within-subject	Smokers	13; M+F; median age 38 (range 23-46)	All smokers switched to e-cig for 14 days.

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7.2. Appendix 2 References of included studies (reference number in brackets)

Xavier RF, Ramos D, Ito JT, Rodrigues FM, Bertolini GN, Macchione M, de Toledo AC, Ramos EM. Effects of cigarette smoking intensity on the mucociliary clearance of active smokers. Respiration. 2013; 86(6):479-85. doi: 10.1159/000348398. Epub 2013 Apr 19. PubMed PMID: 23615315.(12)

Mendes P, Liang Q, Frost-Pineda K, Munjal S, Walk RA, Roethig HJ. The relationship between smoking machine-derived tar yields and biomarkers of exposure in adult cigarette smokers in the US. Regul Toxicol Pharmacol. 2009 Oct; 55(1):17-27. doi: 10.1016/j.yrtph.2009.05.016. Epub 2009 May 28. PubMed PMID: 19481578. (14)

Sakaguchi C, Kakehi A, Minami N, Kikuchi A, Futamura Y. Exposure evaluation of adult male Japanese smokers switched to a heated cigarette in a controlled clinical setting. Regul Toxicol Pharmacol. 2014 Aug; 69(3):338-47. doi: 10.1016/j.yrtph.2014.04.016. Epub 2014 May 10. PubMed PMID: 24819671. (37)

Pezzuto A, Spoto C, Vincenzi B, Tonini G. Short-term effectiveness of smoking-cessation treatment on respiratory function and CEA level. J Comp Eff Res. 2013 May; 2(3):335-43. doi: 10.2217/cer.13.25. PubMed PMID: 24236632. (2)

Ramos EM, De Toledo AC, Xavier RF, Fosco LC, Vieira RP, Ramos D, Jardim JR. Reversibility of impaired nasal mucociliary clearance in smokers following a smoking cessation programme. Respirology. 2011 Jul; 16(5):849-55. doi: 10.1111/j.1440-1843.2011.01985.x. PubMed PMID: 21545372. (18)

Polónia J, Barbosa L, Silva JA, Rosas M. Improvement of aortic reflection wave responses 6 months after stopping smoking: a prospective study. Blood Press Monit. 2009 Apr; 14(2):69-75. doi: 10.1097/MBP.0b013e32832941ea. PubMed PMID: 19305186. (17)

Frost-Pineda K, Zedler BK, Oliveri D, Feng S, Liang Q, Roethig HJ. Short-term clinical exposure evaluation of a third-generation Electrically Heated Cigarette Smoking System (EHCSS) in adult smokers. Regul Toxicol Pharmacol2008;52:104-10. (22)

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Tricker AR, Kanada S, Takada K, Leroy CM, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 5: 8-Day randomized clinical trial in Japan. Regul Toxicol Pharmacol2012;64(2):S54-S63. (20)

Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: eight-day randomized clinical trial in Korea. Regul Toxicol Pharmacol2012 Nov 1;64(2 Suppl):S45-53. (19)

van Staden SR, Groenewald M, Engelbrecht R, Becker PJ, Hazelhurst LT. Carboxyhaemoglobin levels, health and lifestyle perceptions in smokers converting from tobacco cigarettes to electronic cigarettes. S Afr Med J2013;11:865-8. (23)

Wang J, Roethig HJ, Appleton S, Werley M, Muhammad-Kah R, Mendes P. The effect of menthol containing cigarettes on adult smokers' exposure to nicotine and carbon monoxide. Regul Toxicol Pharmacol2010;57:24-30. (15)

Roethig HJ, Zedler BK, Kinser RD, Feng S, Nelson BL, Liang Q. Short-term clinical exposure evaluation of a second-generation Electrically Heated Cigarette Smoking System. J Clin Pharmacol2007;47:518. (32)

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7.3. Appendix 3 Excluded studies from search 1

Literature retrieved using Search 1: To identify literature that linked smoking or nicotine replacement to carboxyhemoglobin using the search string: ((COHb OR carboxyhaemoglobin) AND (smokers OR smoking OR nicotine replacement) AND ("2008"[Date - Publication]: "2014"[Date - Publication]) AND English[Language].

E1. COHb used only as control/biomarker of exposure

McKinney DL, Frost-Pineda K, Oldham MJ, Fisher MT, Wang J, Gogova M, Kobal G. Cigarettes with different nicotine levels affect sensory perception and levels of biomarkers of exposure in adult smokers. Nicotine Tob Res. 2014 Jul; 16(7):948-60. doi: 10.1093/ntr/ntu009. Epub 2014 Mar 17. PubMed PMID: 24638852.

Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. Subst Abuse. 2013 Sep 3; 7:139-46. doi: 10.4137/SART.S12756. eCollection 2013. PubMed PMID: 24049448; PubMed Central PMCID: PMC3772898.

Bailey BA. Using expired air carbon monoxide to determine smoking status during pregnancy: preliminary identification of an appropriately sensitive and specific cut-point. Addict Behav. 2013 Oct; 38(10):2547-50. doi: 10.1016/j.addbeh.2013.05.011. Epub 2013 May 23. PubMed PMID: 23793041.

Schmekel B, Blomstrand P, Venge P. Serum lysozyme - a surrogate marker of pulmonary microvascular injury in smokers? Clin Physiol Funct Imaging. 2013 Jul; 33(4):307-12. doi: 10.1111/cpf.12029. Epub 2013 Feb 15. PubMed PMID: 23692621.

Tricker AR, Kanada S, Takada K, Martin Leroy C, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 6: 6-Day randomized clinical trial of a menthol cigarette in Japan. Regul Toxicol Pharmacol. 2012 Nov 1; 64(2 Suppl):S64-73. doi: 10.1016/j.yrtph.2012.08.007. Epub 2012 Aug 23. PubMed PMID: 22951347.

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Kitahara Y, Hattori N, Yokoyama A, Yamane K, Sekikawa K, Inamizu T, Kohno N. Cigarette smoking decreases dynamic inspiratory capacity during maximal exercise in patients with type 2 diabetes. Hiroshima J Med Sci. 2012 Jun; 61(2):29-36. PubMed PMID: 22916510.

Yarlioglues M, Kaya MG, Ardic I, Dogdu O, Yarlioglues H, Zencir C, Ozdogru M, Akpek M, Kasapkara HA, Sarli B, Duran M, Dogan A, Ozdogru I, Oguzhan A. Dose-dependent acute effects of passive smoking on left ventricular cardiac functions in healthy volunteers. J Investig Med. 2012 Feb;60(2):517-22. doi: 10.231/JIM.0b013e31823e9fb1. PubMed PMID: 22222229.

Jacob P 3rd, Abu Raddaha AH, Dempsey D, Havel C, Peng M, Yu L, Benowitz NL. Nicotine, carbon monoxide, and carcinogen exposure after a single use of a water pipe. Cancer Epidemiol Biomarkers Prev. 2011 Nov; 20(11):2345-53. doi: 10.1158/1055-9965.EPI-11-0545. Epub 2011 Sep 9. PubMed PMID: 21908725; PubMed Central PMCID: PMC3210932.

Muhammad-Kah R, Liang Q, Frost-Pineda K, Mendes PE, Roethig HJ, Sarkar M. Factors affecting exposure to nicotine and carbon monoxide in adult cigarette smokers. Regul Toxicol Pharmacol. 2011 Oct; 61(1):129-36. doi: 10.1016/j.yrtph.2011.07.003. Epub 2011 Jul 21. PubMed PMID: 21798300.

Liu J, Liang Q, Frost-Pineda K, Muhammad-Kah R, Rimmer L, Roethig H, Mendes P, Sarkar M. Relationship between biomarkers of cigarette smoke exposure and biomarkers of inflammation, oxidative stress, and platelet activation in adult cigarette smokers. Cancer Epidemiol Biomarkers Prev. 2011 Aug; 20(8):1760-9. doi: 10.1158/1055-9965.EPI-10-0987. Epub 2011 Jun 27. PubMed PMID: 21708936.

Sokolova-Djokić L, Milosević S, Skrbić R, Salabat R, Voronov G, Igić R. Pulse carboxyhemoglobin-oximetry and cigarette smoking. J BUON. 2011 Jan-Mar; 16(1):170-3. PubMed PMID: 21674871.

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Roth D, Herkner H, Schreiber W, Hubmann N, Gamper G, Laggner AN, Havel C. Accuracy of noninvasive multiwave pulse oximetry compared with carboxyhemoglobin from blood gas analysis in unselected emergency department patients. Ann Emerg Med. 2011 Jul; 58(1):74-9. doi: 10.1016/j.annemergmed.2010.12.024. Epub 2011 Apr 2. PubMed PMID: 21459480.

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Unverdorben M, Mostert A, Munjal S, van der Bijl A, Potgieter L, Venter C, Liang Q, Meyer B, Roethig HJ. Acute effects of cigarette smoking on pulmonary function. Regul Toxicol Pharmacol. 2010 Jul-Aug; 57(2-3):241-6. doi: 10.1016/j.yrtph.2009.12.013. Epub 2010 Mar 15. PubMed PMID: 20233598.

Mendes P, Kapur S, Wang J, Feng S, Roethig H. A randomized, controlled exposure study in adult smokers of full flavor Marlboro cigarettes switching to Marlboro Lights or Marlboro Ultra Lights cigarettes. Regul Toxicol Pharmacol. 2008 Aug; 51(3):295-305. doi: 10.1016/j.yrtph.2008.04.014. Epub 2008 May 11. PubMed PMID: 18565634.

Suner S, Partridge R, Sucov A, Valente J, Chee K, Hughes A, Jay G. Non-invasive pulse CO-oximetry screening in the emergency department identifies occult carbon monoxide toxicity. J Emerg Med. 2008 May; 34(4):441-50. doi: 10.1016/j.jemermed.2007.12.004. Epub 2008 Jan 28. PubMed PMID: 18226877.

Liang Q, Roethig HJ, Lipowicz PJ, Jin Y, Mendes PE. The effect of cigarette burn time on exposure to nicotine and carbon monoxide in adult smokers. Regul Toxicol Pharmacol. 2008 Feb; 50(1):66-74. Epub 2007 Aug 29. PubMed PMID: 17931761.

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E2. COHb lacked link to disease or smoking

Krautter GR, Borgerding MF. Comparison of Consumption Patterns, Biomarkers of Exposure and Subjective Effects in Cigarette Smokers Switched to Dissolvable Tobacco (Camel Orbs), Dual Use, or Tobacco Abstinence. Nicotine Tob Res. 2014 May 30. pii: ntu082. [Epub ahead of print] PubMed PMID: 24879304.

Rodrigues FM, Ramos D, Xavier RF, Ito JT, Souza AP, Fernandes RA, Cecchini R, Rossi e Silva RC, Macchione M, Toledo-Arruda AC, Guarnier FA, Ramos EM. Nasal and systemic inflammatory profile after short term smoking cessation. Respir Med. 2014 Jul; 108(7):999-1006. doi: 10.1016/j.rmed.2014.04.020. Epub 2014 May 9. PubMed PMID: 24863424.

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Minami S, Yamamoto S, Ogata Y, Nakatani T, Takeuchi Y, Hamaguchi M, Koba T, Komuta K. Ambulatory pulse oximetry monitoring in Japanese COPD outpatients not receiving oxygen therapy. Multidiscip Respir Med. 2014 Apr 17; 9(1):24. doi: 10.1186/2049-6958-9-24. eCollection 2014. PubMed PMID: 24739130; PubMed Central PMCID: PMC4021057.

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Sarkar M, Liu J, Koval T, Wang J, Feng S, Serafin R, Jin Y, Xie Y, Newland K, Roethig HJ. Evaluation of biomarkers of exposure in adult cigarette smokers using Marlboro snus. Nicotine Tob Res. 2010 Feb; 12(2):105-16. doi: 10.1093/ntr/ntp183. Epub 2009 Dec 21. PubMed PMID: 20026503.

Gosselin NH, Brunet RC, Carrier G. Determination of carboxyhaemoglobin in humans following low-level exposures to carbon monoxide. Inhal Toxicol. 2009 Nov; 21(13):1077-91. doi: 10.3109/08958370902744848. PubMed PMID: 19852549.

Topacoglu H, Katsakoglou 2, Ipekci A. Effect of exhaust emissions on carbon monoxide levels in employees working at indoor car wash facilities. Hippokratia 2014 Jan;18(1):37-9. PMID: 25125950

E3. Disease not covered by search categories

Kanto-Nishimaki Y, Saito H, Watanabe-Aoyagi M, Toda R, Iwadate K. Investigation of oxyhemoglobin and carboxyhemoglobin ratios in right and left cardiac blood for diagnosis of fatal hypothermia and death by fire. Leg Med (Tokyo). 2014 Jul 5. pii: S1344-6223(14)00096-0. doi: 10.1016/j.legalmed.2014.06.010. [Epub ahead of print] PubMed PMID: 25048514.

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Sebbane M, Claret PG, Mercier G, Lefebvre S, Théry R, Dumont R, Maillé M, Richard JP, Eledjam JJ, de La Coussaye JE. Emergency department management of suspected carbon monoxide poisoning: role of pulse CO-oximetry. Respir Care. 2013 Oct; 58(10):1614-20. doi: 10.4187/respcare.02313. Epub 2013 Mar 19. PubMed PMID: 23513247.

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La Fauci G, Weiser G, Steiner IP, Shavit I. Carbon monoxide poisoning in narghile (water pipe) tobacco smokers. CJEM. 2012 Jan; 14(1):57-9. Review. PubMed PMID: 22417961.

Hoff CM, Grau C, Overgaard J. Effect of smoking on oxygen delivery and outcome in patients treated with radiotherapy for head and neck squamous cell carcinoma--a prospective study. Radiother Oncol. 2012 Apr; 103(1):38-44. doi: 10.1016/j.radonc.2012.01.011. Epub 2012 Mar 3. PubMed PMID: 22385797.

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Sen S, Peltz C, Beard J, Zeno B. Recurrent carbon monoxide poisoning from cigarette smoking. Am J Med Sci. 2010 Nov; 340(5):427-8. doi: 10.1097/MAJ.0b013e3181ef712d. PubMed PMID: 20739872.

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Leifert JA. Anaemia and cigarette smoking. Int J Lab Hematol. 2008 Jun; 30(3):177-84. doi: 10.1111/j.1751-553X.2008.01067.x. Review. PubMed PMID: 18479294.

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Theron A, Schultz C, Ker JA, Falzone N. Carboxyhaemoglobin levels in water-pipe and cigarette smokers. S Afr Med J. 2010 Jan 29;100(2):122-124. PMID: 20459918

E4. Studies of passive or parental smoking

Dogan A, Yarlioglues M, Gul I, Kaya MG, Ozdogru I, Kalay N, Inanc MT, Ozdogru M, Ardic I, Dogdu O, Eryol NK, Ergin A, Oguzhan A. Acute effects of passive smoking on left ventricular systolic and diastolic function in healthy volunteers. J Am Soc Echocardiogr. 2011 Feb; 24(2):185-91. doi: 10.1016/j.echo.2010.10.019. Epub 2010 Dec 10. PubMed PMID: 21145704.

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E5. Studies in narrow population (e.g. pregnant women)

da Silva LA, Robazzi ML, Terra Fde S. Relation between workplace accidents and the levels of carboxyhemoglobin in motorcycle taxi drivers. Rev Lat Am Enfermagem. 2013 Sep-Oct; 21(5):1119-26. doi: 10.1590/S0104-11692013000500015. English, Portuguese, Spanish. PubMed PMID: 24142221.

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E7. Toxicological or forensic measurement

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E8. Studies with no comparison to smoking and cessation/switching

Roethig HJ, Munjal S, Feng S, Liang Q, Sarkar M, Walk RA, Mendes PE. Population estimates for biomarkers of exposure to cigarette smoke in adult U.S. cigarette smokers. Nicotine Tob Res. 2009 Oct; 11(10):1216-25. doi: 10.1093/ntr/ntp126. Epub 2009 Aug 21. PubMed PMID: 19700523.

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E9. COHb not measured or presented as AUC

Sarkar M, Kapur S, Frost-Pineda K, Feng S, Wang J, Liang Q, Roethig H. Evaluation of biomarkers of exposure to selected cigarette smoke constituents in adult smokers switched to carbon-filtered cigarettes in short-term and long-term clinical studies. Nicotine Tob Res. 2008 Dec; 10(12):1761-72. doi: 10.1080/14622200802443718. PubMed PMID: 19023827.

Roethig HJ, Feng S, Liang Q, Liu J, Rees WA, Zedler BK. A 12-month, randomized, controlled study to evaluate exposure and cardiovascular risk factors in adult smokers switching from conventional cigarettes to a second-generation electrically heated cigarette smoking system. J Clin Pharmacol. 2008 May; 48(5):580-91. doi: 10.1177/0091270008315316. Epub 2008 Mar 4. PubMed PMID: 18319361.

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7.4. Appendix 4 Excluded studies from search 2

Search 2: To identify literature reporting an association between carboxyhaemoglobin and cardiovascular disease using the search string: (COHb OR carboxyhaemoglobin) AND (cardiovascular disease AND association) AND ("2008"[Date - Publication]: "2014"[Date - Publication]) AND English[Language].

E2. COHb lacked link to disease or smoking

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Rylance J, Gordon SB, Naeher LP, Patel A, Balmes JR, Adetona O, Rogalsky DK, Martin WJ Household air pollution: a call for studies into biomarkers of exposure and predictors of respiratory disease. 2nd. Am J Physiol Lung Cell Mol Physiol. 2013 May 1; 304(9):L571-8. doi: 10.1152/ajplung.00416.2012. Epub 2013 Mar 1. PMID: 23457186

Sari I, Zengin S, Ozer O, Davutoglu V, Yildirim C, Aksoy M. Chronic carbon monoxide exposure increases electrocardiographic P-wave and QT dispersion. Inhal Toxicol. 2008 Jul; 20(9):879-84. doi: 10.1080/08958370801958622 . PMID: 18645728

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7.5. Appendix 5 Excluded studies from search 3

Search 3: To identify literature reporting an association between carboxyhaemoglobin and respiratory disease using the search string: (COHb OR carboxyhaemoglobin) AND (respiratory disease AND association) AND ("2008"[Date - Publication]: "2014"[Date - Publication]) AND English[Language].

E2. COHb lacked link to disease or smoking

Rylance J, Gordon SB, Naeher LP, Patel A, Balmes JR, Adetona O, Rogalsky DK, Martin WJ 2nd Household air pollution: a call for studies into biomarkers of exposure and predictors of respiratory disease. Am J Physiol Lung Cell Mol Physiol. 2013 May 1; 304(9):L571-8. doi: 10.1152/ajplung.00416.2012. Epub 2013 Mar 1. PMID: 23457186

Zavorsky GS, Blood AB, Power GG, Longo LD, Artal R, Vlastos EJ. CO and NO pulmonary diffusing capacity during pregnancy: Safety and diagnostic potential. Respir Physiol Neurobiol. 2010 Mar 31; 170(3):215-25. doi: 10.1016/j.resp.2010.02.001. Epub 2010 Feb 10. Review.PMID: 20149901

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Baldi S, Pinna GD, Mombaruzzo P, Biglieri M, De Martini A, Palange P. C-reactive protein correlates with tissue oxygen availability in patients with stable COPD. Int J Chron Obstruct Pulmon Dis. 2008; 3(4):745-51. PMID: 19281089

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