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August 15, 2014.

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This report is in response to your request for my review of the document titled "Appendix A to Comments of National Federation of Federal Employees, Drug Policy Alliance, and DKT Liberty Project regarding Proposed Revisions to Mandatory Guidelines for Federal Workplace Drug Testing Programs, FR DOC #04-7984, SAMHSA, HHS ". I am familiar with this document and briefly review it herein.

I note that this document was submitted in response to a request for comments on Proposed Rules published by the Substance Abuse and Mental Health Services Administration (SAMHSA) in the Federal Register . The Appendix A was an attachment to a 4-page letter dated July 12, 2004 by the National Federation of Federal Employees, the Drug Policy Alliance and the DKT Liberty Project. It was addressed to Walter Vogl, Ph.D., Drug Testing Section, Division of Workplace Programs, Substance Abuse and Mental Health Services Administration, Department of Health and Human Services. The letter was regarding: Proposed Revisions to Mandatory Guidelines for Federal Workplace Drug Testing Programs, FR DOC #04-7984, SAMHSA, HHS. The cover letter addresses several aspects of the Proposed Revisions, including sweat testing. I have included the cover letter below.

The Appendix A was titled " THE SCIENTIFIC ISSUE: HOW ACCURATE ARE POSITIVE SWEAT PATCH TEST RESULTS AS AN INDICATOR OF RECENT DRUG USE BY THE TEST SUBJECT?"

Overall, the Appendix authors comment on the results from six published studies: three laboratory-based studies and three field (observational) studies. In addition, the authors comment on the supposed results from supposed unpublished studies supposedly performed by PharmChem. I use the term "supposed" because, in my opinion, these documents have an insufficient indicia of scientific authorship, lack a clearly

documented connection between test results and experimental details, and lack a clearly documented connection between test results and any interpretation and conclusions. The Appendix authors also include citations to two additional published studies and one oral presentation, on which I comment. The Appendix authors claim that these studies demonstrate that the sweat patch is unreliable, generating false positive test results; an opinion with which I disagree on scientific grounds after my review of the cited studies as well as the large body of other relevant published scientific studies.

The Appendix authors indicate that research has established beyond a doubt that the sweat patch is susceptible to environmental contamination. But the Appendix authors neglect to specify the experimental conditions under which such "environmental contamination" was demonstrated, a critical issue. The Appendix authors indicate that a subject's skin can be contaminated with drugs prior to attachment of the patch, but again neglect to provide the experimental details for such skin contamination. The Appendix authors indicate that drugs can penetrate the outside of the patch, but again neglect to specify the experimental details for such observations. The Appendix authors claim that each of these scenarios would lead to "positive" test results, but omit the details of the laboratory criteria specified for reporting a test result as "positive" which include criteria beyond simply finding a drug present in the sweat patch above a specific concentration.

In contrast to the opinions of the Appendix authors, my review of the cited studies and many others published in the peer-reviewed literature, including many published since the six studies cited in the Appendix which dated from 1999 to 2003, demonstrates that the sweat patch is in fact a reliable and accurate drug test device. In my opinion, the Appendix authors have misconstrued what the six cited studies actually demonstrated and what they did not demonstrate.

At the outset of the Appendix, the Appendix authors list six bulleted points, summarized below, to which I have added my brief comments.

• Studies find a substantial numbers of false positives

None of the studies cited by the authors have convincingly demonstrated that any positive sweat patch test results for donors wearing a sweat patch are in fact "false", i.e. that the donors did not actually use drugs. The cited studies never definitively proved that those wearing sweat patches did not in fact use drugs.

• That environmental contamination can cause a false positive is well-established

No study of subjects wearing sweat patches has definitively proven that any positive patch results obtained were in fact false and due to non-laboratory environmental contamination. Although laboratory studies (i.e. where sweat patches were applied to Petri dishes, not worn by human subjects) have demonstrated that drugs may penetrate the outside of the patch under certain specific laboratory conditions, this has been demonstrated only under laboratory conditions which, in my opinion, are unrealistic in any natural normal real-life scenario.

• Long-term storage of drugs in skin can cause a false positive

The studies addressing drug storage in skin and subsequent sweat patch testing used, in my opinion, unrealistic impregnation of subjects' skin with drugs before patch application. One study cited by the Appendix authors merely detected drugs in post-mortem tissue specimens, but that study's authors only speculated that such tissue presence of drugs from prior drug use could cause a positive sweat patch test result.

• False positives have occurred in both real-world as well as laboratory studies

No real-world study has ever definitively shown that positive sweat patch test results for human subjects wearing sweat patches were in fact false, because the studies never definitively proved that the subjects did not actually use the drugs. Laboratory studies claiming positive patch results after intentional external contamination of the patch itself or intentional prior skin contamination with applied drugs have been performed in unrealistic conditions unlikely to be encountered in a normal real-life setting.

• No scientific consensus on patch reliability

There have been over 50 papers in the peer-reviewed published clinical and scientific literature from research centers world-wide finding the sweat patch to be an accurate and reliable device. Only a few studies have been critical of the accuracy of the sweat patch and these were all published at least 10 years ago, with numerous studies since then finding the patch to be reliable. In 2004, the U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, published in the Federal Register their review of the clinical and scientific literature addressing the sweat patch, including those few studies critical of the sweat patch. This review indicated "Also, scientific advances in the use of head hair, sweat, and oral fluid in detecting drugs have made it possible for these specimens to be used in Federal programs with the same level of confidence that has been applied to the use of urine." SAMHSA, Federal Register, 4/13/04, 69 FR 19689.

• No general acceptance within the forensic toxicology community

As noted above, there have been at least 50 papers in the peer-reviewed published clinical and scientific literature from research centers world-wide finding the sweat patch to be an accurate and reliable device. The U.S. Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, in reviewing the published clinical and scientific literature indicated "Also, scientific advances in the use of head hair, sweat, and oral fluid in detecting drugs have made it possible for these specimens to be used in Federal programs with the same level of confidence that has been applied to the use of urine." SAMHSA, Federal Register, 4/13/04, 69 FR 19689.

Below, I review the Appendix authors' comments about each of the six cited published studies and what was actually presented and scientifically demonstrated in the studies' reports.

A. "Real-Life" studies.

The Appendix authors label their review of three field studies as "real life" studies.

In this section the Appendix authors comment on three studies:

• The Naval Research Laboratory 2003 study – Real-life comparison of patch and urine test results.
(published as D. Kidwell et al., Comparison of daily urine, sweat, and skin swabs among cocaine users, For. Sci. Int., 133, 63 (2003)).

• The Preston comparison study: Real-life comparison of patch and urine test results
(published as K. Preston et al., Monitoring cocaine use in substance-abuse treatment patients by sweat and urine testing, J. Anal. Toxicol., 23, 313 (1999)).

• The Levisky comparison study – Real-life comparison of patch to urine test results
(published as J. Levisky et al., Comparison of urine to sweat patch test results in court ordered testing, For. Sci. Int., 122, 65 (2001)).

The Appendix authors indicate that these "real-life" studies compared sweat patch results with urine test results and found false positive sweat patch results, i.e. according to the definition of a false positive sweat result as one associated concomitant "negative" urine drug test results. However, the Appendix authors mistakenly presume that the "negative" urine test results are definitive proof that those patch wearers did not use any drug. However, upon close examination of the studies' experimental details, none of these studies definitively demonstrated that the "real-life" subjects who had the claimed "false positive" sweat patch results actually never used the drugs in question. The reported "negative" urine test results as performed and reported cannot be taken to be dispositive that there was no drug use. Simply reporting urine drug test results as "negative" can not be taken as proof that there has not been drug use. Urine tests must be performed frequently enough (i.e. daily), using highly-sensitive cutoffs (e.g. at the laboratory's Limit of Detection) and taking into detailed account the extent of any urine dilution (i.e. through creatinine or specific gravity measurements) in order to be certain that any instances of drug use are effectively detected through urinalysis. Absent such rigorous and detailed urine drug testing, "negative" urine drug test results cannot be taken as definitive proof that there has not been any drug use. Thus, none of the cited "real-life" studies definitively proved that the patch-wearing subjects with claimed "false positive" sweat patch results did not in fact use any drugs. Thus, positive sweat patch results with associated "negative" urine test results do not prove that the positive sweat patch results were in fact false positives. The patch wearers in these studies could have actually used some drug, and accordingly had true positive sweat patch test results, but where such drug use was not detected through the urine drug testing as performed.

Below I briefly review of each of the cited studies and what the Appendix authors have claimed about what the studies show and what each study actually did or did not demonstrate.

D. Kidwell et al., Comparison of daily urine, sweat, and skin swabs among cocaine users, For. Sci. Int., 133, 63 (2003).

This study of 10 subjects undergoing treatment for cocaine dependence claimed to demonstrate a 7% rate of false positive sweat patch test results where the associated urine specimens apparently showed no evidence of drug use, with environmental contamination claimed as the basis for the positive patches. This incompletely controlled field study, although apparently well-intentioned, has numerous scientific shortcomings, including incomplete provision of all data for all subjects, as well as apparent typographical errors making a clear understanding of the actual experimental details and associated test results challenging. The authors claimed 7 false positive sweat patch results. However, data for only 5 of these were presented in the paper. At least 3 of the 7 positive sweat patch results which were labeled as "false positives" because of associated "negative" urine test results, were actually associated with elevated urine benzoylecgonine (cocaine metabolite) concentrations which clearly indicate the potential for actual drug use rather than innocent environmental exposure. The criteria used by the study authors for labeling sweat patch results as "positive" involved only a measure of cocaine alone and did not include any requirement for the presence of its metabolite, benzoylecgonine, as currently specified for the laboratory to report a sweat patch positive for cocaine.

The Appendix authors claim that for drug abstinent subjects false positive sweat patch results were obtained 7% of the time. But, in fact, there was never any proof in the study that the subjects in question were in fact completely drug abstinent. The urine testing was not performed frequently enough (i.e. truly daily) to effectively identify any drug use. Nor was the urine testing performed at the laboratory's more sensitive Limit of Detection, instead using a less sensitive 300 ng/mL urine cocaine metabolite cutoff for defining whether there was or was not any drug use and accordingly labeling sweat patch results as false positive. Nor was urine creatinine taken fully into account (actual creatinine concentrations were not presented). Accordingly, the "negative" urine test results cannot be taken as proof that the subjects were in fact drug abstinent. Thus, both the Appendix authors and the study authors have not proven that any positive sweat patch results for those subjects were in fact "false". The "negative" urine tests do not prove that the subjects did not use any drug.

The Appendix authors, as well as the study authors, emphasize that subjects were given daily urine tests. However, a close reading of the study's experimental details indicates that, in fact, the subjects were not given daily urine tests every day of the study (as the word "daily" would imply). The study details demonstrate that there were no urine tests given on Sundays or on a single Thursday holiday, thereby allowing for cocaine use that may not have been detected by the urine tests as performed, but could lead to true positive sweat patch test results. Accordingly, participants would have been tested on Saturday morning and not tested again until Monday morning, clearly allowing an opportunity to use some cocaine and perhaps avoid detection of such use through urine testing as performed. The published literature demonstrates examples of participants in controlled cocaine-dosing studies with negative urine test results within 48 hr after use. Thus, the study as performed did not definitively demonstrate that those subjects with claimed false positive sweat patch test results did not in fact use cocaine.

The Appendix authors also rely on the detection of cocaine in isopropanol skin swabs to support the claimed potential for environmental contamination. Although cocaine was found on the skin of some subjects, there was no demonstration in the study that such external skin contamination was in fact responsible for any of

the positive sweat patch results. There was no demonstration of whether the subjects' environments were or were not actually "contaminated" with cocaine, whether any such potential environmental cocaine actually transferred to the subjects, nor any demonstration whether such potentially contaminated environments led to positive sweat patch test results.

Thus, although the Appendix authors rely on this study to claim that false positive sweat patch results were demonstrated for subjects in a "real-world" setting, in fact the study never definitively demonstrated that the claimed false positive sweat patches were in fact false, i.e. the study never definitively demonstrated that the subjects in question did not actually use cocaine that was not detected by the less-than-optimal urine testing. In summary, although this study claims to demonstrate false positive sweat patch results in "real life" environmental exposure situations, the study's shortcomings preclude giving much weight to those interpretive claims, especially when several of the claimed false positive sweat patch results clearly had evidence of actual drug use in the associated urine specimens.

K. Preston et al., Monitoring cocaine use in substance-abuse treatment patients by sweat and urine testing, J. Anal. Toxicol., 23, 313 (1999).

This study compared sweat patch test results with associated urine testing over 17 weeks for 44 subjects in a methadone maintenance program.

In this study, only 3 urine specimens were collected during each week-long patch wear period. It is critical to the interpretation of the study results to note that the urine specimens were not collected each day during patch wear, but rather every other day, except on week-ends, where there was a 2-day period during patch wear without urine collections. Thus, there were a total of 4 days during the week-long patch wear period where no urine specimens were collected, including one 2-day week-end without any urine specimen collection. The study authors chose to define any sweat patch positive result without any accompanying urine positive results as a "false positive" patch result. This is an unfortunate choice of performance criteria as it is certainly possible that a subject could actually use cocaine during the period of patch wear and yet not have a urine specimen collected that day or for even two days over the weekend. Accordingly, the patch could yield a true positive result even though the too-widely spaced urine specimens tested "negative". Thus, the urine testing was not performed in a sufficiently rigorous manner to effectively identify any drug use.

In the comparison of sweat patch test results with urinalysis the study utilized an ELISA immunoassay cutoff of 10 ng/mL for reporting a sweat patch as positive, although current laboratory procedures utilize a 10 ng/mL GC/MS cutoff. Also, the study found that of 499 sweat patch specimens which were further tested by GC/MS and were found positive at a 5 ng/mL cutoff, 111 (22%) of those were found positive for only cocaine (but not for the cocaine metabolite). Under current laboratory sweat patch reporting procedures for cocaine, none of these 111 would have been reported as positive, as current reporting procedures also require that the presence of the cocaine metabolite, benzoylecgonine, be demonstrated. Thus, the study labeled many sweat patches as positive which would not have been reported positive under current laboratory reporting procedures.

In comparing a subset of 355 matched sweat and urine specimens, 21.1% of sweat patch results were labeled as "false positives". But, as noted above, the sweat patches were reported as positive using a 10 ng/mL immunoassay cutoff, not a 10 ng/mL GC/MS cutoff, and without any requirement for the presence of the cocaine metabolite (note that the study also found that 22% of GC/MS positive patches at a 5 ng/mL cutoff were positive for cocaine only and thus would not be reported positive using current reporting criteria). Further studies of a subset of apparent "false positive" sweat patch pairs demonstrated that half of paired sweat patches were below the ELISA immunoassay reporting cutoff of 10 ng/mL and thus would not have been reported as positive under current reporting criteria. Thus, at least some of the so-labeled "false positive" positive sweat patches would not have been reported as positive under current laboratory reporting criteria. Furthermore, the associated urine specimens were reported as positive or negative using a 300 ng/mL immunoassay cutoff, and not using the laboratory's more sensitive Limit of Detection. Furthermore, further examination of urine specimens associated with some of the claimed false positive patches demonstrated that 40% of those actually had cocaine metabolite detectable at a lower 30 ng/mL cutoff vs. the 300 ng/mL cutoff used to label urine specimens as positive or negative. Also, the study did not further examine the urine test results according to creatinine or specific gravity to control for any specimen dilution. Thus, some of the claimed "false positive" sweat patches may have actually had associated urine specimens

demonstrating the presence of cocaine metabolite and accordingly demonstrating use. Thus, at least some number of the reported "false positive" sweat patches would have not been reported as positive nor were the associated claimed "negative" urine specimens actually drug-free.

The Appendix authors claim that this study demonstrated a substantial number of "false positive" sweat patch results because of associate "negative" urine test results. However, the study never definitively demonstrated that those subjects with the claimed "false positive" sweat patches did not in fact use cocaine.

The Appendix authors claim that the study was "designed to ensure that urine test would detect any drug use". However, the urine testing was not performed in such a manner as to preclude any possible drug use that could lead to a positive sweat patch test result. The Appendix authors claim in a footnote that some urine specimens were tested at the Limit of Detection, but the study does not indicate that it ever utilized the laboratory's Limit of Detection for the analysis of the cocaine metabolite in urine in the overall comparison of sweat patch and urine testing. The urine cutoff was lowered from 300 to 30 ng/mL in the analysis of a subset of urine specimens associated with claimed "false positive" patches, and that analysis demonstrated that 40% of those specimens in fact had cocaine metabolite between the 300 and 30 ng/mL immunoassay cutoff. Thus, simply relying on a less sensitive 300 ng/mL urine cutoff to define whether or not a sweat patch should be considered a "false positive" is not sufficiently rigorous in identifying any drug use.

The Appendix authors speculate that because the subjects were known drug users their home environments may have been contaminated with drugs. Although this may be true, there was no demonstration in the study that any of the subjects' home environments were in fact contaminated with cocaine. Furthermore, I am unaware of any study that has demonstrated that a home environment shown to be contaminated with cocaine has led to a positive sweat patch test for a subject wearing a sweat patch in such an environment, as a result of a subject's exposure to such a contaminated environment, whether by ingestion of, exposure of the skin to, or exposure of the outside of the patch to such environmental contamination.

The Appendix authors misconstrue the periodic "negative" urine test results as demonstrating that the subjects had in fact abstained from cocaine use. The urine testing was not performed in a such a manner to make such a definitive showing of abstinence from any drug use, nor did the study authors make any such claim that "negative" urine test results proved that subjects had in fact abstained from all use of cocaine.

Thus, the study did not convincingly demonstrate that any of the claimed "false positive" sweat patches with associated "negative" urine test were in fact for subjects who did not use any cocaine. The study never demonstrated complete abstinence in its subjects.

The study authors themselves acknowledged that the sweat patches labeled as "false positives" may in fact be true positives, with sweat patch testing being more sensitive at detecting cocaine use than urine. They stated "The majority of sweat patches found positive for cocaine by ELISA in the absence of cocaine-positive urine were confirmed positive by GC-MS, suggesting that the occasions of drug use detected with sweat but not urine testing were true positives.

It should be noted that the study authors concluded "In summary, sweat testing provides a useful alternative for monitoring drug usage."

J. Levisky et al., Comparison of Urine Sweat Patch Test Results in Court Ordered Testing, J. For. Sci., 122, 65 (2001).

This study involved a single subject and compared several sweat patch test results with accompanying periodic urine test results. The study authors claimed that instances of positive sweat patches with associated "negative" urine specimens indicate that the positive sweat patch results were "false positives". There were 5 sweat patches with positive test results, but the study authors addressed only three patches which were positive for cocaine alone, with all accompanying urine specimens reported "negative".

The authors state that "With the exception of 1 day during this period, the subject was continuously monitored." An examination of the graphical timeline shows that throughout the study period there was always a patch being worn (except for 1 day). The authors indicate that over a 170-day period, 104 urine specimens were obtained. Thus, the subject was monitored through urine testing only 61% of the days. It is clear from the timeline chart presented in the paper that while there was regular daily urine testing during weekdays, there was no urine testing during the weekend. Thus, it is entirely possible that the subject could have used drugs during the weekend leading to a true positive sweat patch test result while subsequent urine specimens collected after the weekend could be reported "negative". It has been demonstrated in the literature that cocaine can be readily eliminated over 1–2 days with subsequent "negative" urine test results. Also, examination of the timeline indicates that there were numerous days when there was neither urine testing nor a patch being worn.

The urine test results were reported as simply "negative" using a 300 ng/mL cut-off for the cocaine metabolite, benzoylecgonine. However, the urine test results may actually have demonstrated the presence of these drugs/metabolites, but simply less than the administrative cut-off. One must also be careful to distinguish a "negative" result from "no drugs present" or detected. Thus, such "negative" urine test results cannot be interpreted to demonstrate that there has been no drug use and thereby impugn the positive sweat patch test results as "false positives". Furthermore, no information was provided as to the extent of any dilution of the urine specimens (e.g. through creatinine and/or specific gravity measurements).

The authors conclude that the positive patch results for three patches (worn 3/22-4/4, 4/4–4/18, 5/2–5/16) are false positives because the urine specimens collected during patch wear period were "negative". For the patch worn from 3/22–4/4, urine specimens were collected on weekdays for 10 of the 14 days. There were 2 weekends where no urine specimens were collected. For the patch worn from 4/4–4/18, urine specimens were collected for 11 of the 15 days. There were 2 weekends where no urine specimens were collected. For the patch worn from 5/2–5/16, urine specimens were collected for 11 of the 15 days. There were 2 weekends where no urine specimens were collected. It is entirely possible and consistent with what is known about cocaine pharmacokinetics that the subject could have used cocaine over these weekends in sufficient amounts to test positive in the sweat patch and yet eliminating sufficient drug such that subsequent urine tests on Monday were negative at the administrative reporting cutoff. Furthermore, any effort by the subject at dilution of the urine specimens e.g. through excess fluid consumption, could also have minimized the likelihood of testing positive.

The Appendix authors cite this study as an example of false positive sweat patch test results because of associated "negative" urine test results. However, the study did not actually demonstrate that the positive sweat patch test results were actually false, i.e. the study did not prove that the subject did not use any cocaine. The study did not perform urine testing sufficiently frequently, nor at a sensitive Limit of

Detection, nor taking dilution into account. Thus, the "negative" urine test results do not demonstrate abstinence and accordingly do not impugn the positive sweat patch test results.

B. Laboratory Studies

In this section the Appendix authors review three published and one unpublished laboratory-based studies:

• The Naval Research Laboratory 2001 Study
D. Kidwell and F. Smith, Susceptibility of PharmChek™ Drugs of Abuse Patch to Environmental Contamination, For. Sci. Int'l., 116, 89 (2001). Also published earlier as Naval Research Laboratory report NLR/MR/6170--99--8414 (11/3/99).

• The Crouch environmental contamination study
(published as D. Crouch et al., An Assessment of the Effectiveness of the PharmChek™ Sweat Patch Skin Cleansing Procedures, Bull. Int. Ass'n. For. Toxicol., 32 (2), 5–8 (2002)).

• The skin storage study
(published as J. Levisky et al., Drug deposition in adipose tissue and skin: Evidence for an alternative source of positive sweat patch tests, For. Sci. Int., 110 (1), 35 (2000)).

• PharmChem's Internal Studies
(unpublished and unsubstantiated)

At the outset of this section, the Appendix authors make claims about what PharmChem officials supposedly testified in court about the reliability of the sweat patch, but the Appendix authors have not provided any citations or quotes from actual courtroom testimony transcripts to demonstrate what in fact has or has not been claimed by PharmChem officials in courtroom testimony.

Below I review of each of the four cited laboratory studies and what the Appendix authors have claimed about what the studies show and what each study actually did or did not demonstrate.

D. Kidwell and F. Smith, Susceptibility of PharmChek™ drugs of abuse patch to environmental contamination, For. Sci. Int'l., 116, 89 (2001). Also published earlier as Naval Research Laboratory report NLR/MR/6170--99--8414 (11/3/99).

This study was performed under laboratory experimental conditions. The study examined whether drugs applied to the outside of sweat patches (patches placed on Petri dishes, not worn by subjects) could penetrate through the patch outer membrane. The study authors describe these experiments as "external contamination". The study also examined whether drugs in solution applied onto subjects' skin could later be detected upon application of the sweat patch. The study authors described these experiments as "internal contamination".

External contamination

It is critical to note that the external contamination of sweat patches was not performed while sweat patches were actually worn by human subjects, but rather when the sweat patches were applied to Petri dishes and kept in a sealed bag in a humid and warm environment. Furthermore, the sweat patches were wetted on the inside by an artificial sweat but with a pH lower than typical human sweat, as well as having the drugs in solutions of varying pH applied to the outside of the patch. The study did demonstrate that under certain experimental laboratory conditions that drugs in specific pH solutions applied to the outside of the patch could penetrate the outer patch membrane and subsequently be detected in the sweat patch inner absorbent pad. However, the study did not utilize the current laboratory criteria for reporting positive test results. For cocaine, it is not sufficient to simply find cocaine in a sweat patch above the reporting cutoff; the metabolite of cocaine, benzoylecgonine, must also be found. Similarly, for reporting test results as positive for methamphetamine, the metabolite, amphetamine, must also be found. These external contamination studies did not clearly demonstrate that cocaine applied to the outside of the patch was converted to some degree to its metabolite, nor did the study clearly indicate that the metabolite itself was applied to the outside of the patch and found to migrate through the patch outer membrane. Similarly, for methamphetamine, there was no demonstration that its metabolite, amphetamine, was found in the patch after application of methamphetamine. The study only demonstrated that methamphetamine could migrate through the patch outer membrane under certain experimental conditions, but the study did not demonstrate that amphetamine was formed after methamphetamine entered the patch. Thus, although the parent drug was detected in the patches after external contamination, these patches would not have been reported as positive under the current specified laboratory reporting criteria.

It is also important to note that penetration of externally applied drug into the patch inner pad occurred only under certain specific experimental conditions of a certain pH solution wetted inside the patch (more acidic than typical human sweat) and the drug applied in solution at certain pHs (with higher basic pHs required for penetration).

Thus, the study does demonstrate the possibility of drug migration through the patch outer membrane under certain specific laboratory conditions. Whether such conditions may ever exist for a human subject wearing a sweat patch in a normal daily environment would need to be demonstrated before a positive sweat

patch test result could be considered possible from such external contamination scenarios. Furthermore, sweat patch test results for cocaine and methamphetamine are reported as positive only if their respective metabolites are also present. The study did not demonstrate that their experimental results would lead to reportable positive test results.

The Appendix authors claim that the study shows that drugs in the environment can permeate the patch. But the study did not actually study drugs "in the environment" but rather drugs in certain pH solutions applied to the outside of sweat patches under certain laboratory conditions. There was no demonstration in this study of anyone actually wearing a sweat patch in a demonstrated drug-contaminated environment and subsequently had drugs detected in their patch or that a reportable positive sweat patch test result occurred from exposure to such a demonstrated drug-contaminated environment.

The Appendix authors indicate that when the exterior of the patch becomes wet with either sweat or tap water that methamphetamine can permeate the outer membrane in amounts large enough to cause positive test results. The Appendix authors however do not note the study's demonstration of the importance of a high pH in the penetration of methamphetamine (and for cocaine as well). Furthermore, although methamphetamine penetrated the patch under certain specific experimental conditions, none of such patches would have been reported as positive under current specified reporting criteria because none of the methamphetamine metabolite, amphetamine, was demonstrated to be present from external contamination by methamphetamine.

In addressing the issue of the pH of common soaps and shampoos, the Appendix authors cite a meeting abstract which addressed the effect of various shampoos on subsequent cocaine uptake in hair after soaking the shampooed hair for eight hours in a cocaine solution. The cited reference (an oral presentation at a scientific meeting) dealt with hair, which is a complex, predominantly protein matrix, whereas the sweat patch has a polyurethane outer membrane. The abstract does not provide any information about the pH of shampoos, although such information may have been presented by the speaker. It does not appear that the results of the orally-presented study were ever published in the peer-reviewed literature. The relevance of the effect of the various shampoos on subsequent drug absorption in hair to sweat patch testing is unclear, and the abstract alone does not provide any information to demonstrate its relevance to sweat patch testing.

Finally, in SAMHSA's 2004 proposal to incorporate sweat patch testing in federal workplace drug testing programs, as published in the Federal Register, SAMHSA indicated "Based on that information, the Department believes that external absorption of any drugs through the outer layer is not possible under normal circumstances." SAMHSA, Federal Register, 4/13/04, 69 FR 19676

Internal contamination

In another set of contamination experiments, drugs were applied in alcohol solution to apparently a single subject's skin which had been pre-cleaned with isopropyl alcohol swabs (twice) and the applied drug solution allowed to penetrate the skin over various periods of time. Thereafter, including normal hygiene, upon application of sweat patches using the standard sweat patch application skin cleaning procedures, the solution-applied drugs could be detected in the sweat patches. For methamphetamine, no amphetamine was found and accordingly no positive patch results would be reported under the specified laboratory reporting criteria. However, for cocaine, after skin application, its metabolite was also detected. However, I note that other reports, including an earlier report co-authored by one of this study's authors, indicate that cocaine is

stable on the skin. But the relevance of these intentional skin contamination experiments using drugs applied in alcoholic solution to any human real-life scenario must be questioned. In fact, the authors themselves acknowledge that such alcoholic solution drug impregnation of skin was "not likely to occur in the real world".

D. Crouch et al., An assessment of the effectiveness of the PharmChek™ sweat patch skin cleansing procedures, Bull. Int. Ass'n. For. Toxicol., 32 (2), 5–8 (2002).

Similar to the previous study addressing in part skin contamination by solution-applied drugs, another study of skin contamination by solution-applied drugs was performed at the Center for Human Toxicology, University of Utah. In this study, 10 human subjects' pre-cleaned skin was treated with sprayed-on solutions of cocaine and methamphetamine and subsequently subjected to sweat patch testing. This included the standard procedure utilized before sweat patch application of swabbing the skin with isopropanol wipes. In spite of spraying onto the skin amounts of cocaine and methamphetamine up to 100 times greater than that necessary for reporting a sweat patch test result as positive, no positive sweat patch result would have been reported based on the specified laboratory criteria for reporting positive test results. Although small amounts of the drugs could be detected in the sweat patches, and, in only a few cases, above the parent drug reporting cutoff, none of the sweat patches would have been reported by the laboratory as "positive" because they all failed to meet the established laboratory criteria for reporting test results as positive, i.e. requiring the presence of the associated metabolites.

In commenting on this study, the Appendix authors indicate that the isopropanol wipes used prior to sweat patch application did not remove all the drug from the skin. This is of no import as none of the subjects ever had a sweat patch result that would have been reported as positive.

Again, it is important to note that these skin "doping" experiments represent artificial impregnation of pre-cleaned skin with drugs applied in solution. The outermost layer of the skin, the stratum corneum, is one of the most impermeable biological membranes known. Drugs from the environment do not easily transfer to the skin, nor easily penetrate the skin. Thus, the relevance of these artificial skin doping experiments to actual subjects wearing sweat patches in their normal environments has to be questioned. In any event, none of Dr. Crouch's skin doping experiments ever led to a sweat patch result which met the criteria for being reported as "positive."

J. Levisky et al., Drug deposition in adipose tissue and skin: Evidence for an alternative source of positive sweat patch tests, For. Sci. Int., 110 (1), 35 (2000).

The authors of this study questioned whether it was possible for previous drug use leading to drug residing in the skin could lead to a subsequent positive sweat patch test result.

This study addressed the presence of drugs in post-mortem skin and adipose tissue specimens obtained during autopsy. The study did not involve any living human subjects wearing sweat patches. The post-mortem tissue specimens were extracted and the level of drugs determined. In three cases, both cocaine and its metabolite, benzoylecgonine, were found in adipose tissue. Cocaine was also found in the three matching skin specimens, but testing for the cocaine metabolite was not performed on the skin specimens. The authors suggested that transfer of drugs from such adipose and skin depots could possibly result in the drugs showing up in sweat patches. Furthermore, the authors postulated that if the kinetics of such transfers out of such tissue deposits were slow, then positive patch test results might occur even though there had not been new drug usage.

Although this study demonstrates the presence of cocaine and its metabolite in post-mortem adipose tissue and skin, it provides no information on the kinetics of such storage in living subjects, nor the likelihood or specific mechanisms of the transfer or diffusion of cocaine or its metabolite to the skin surface or sweat and ultimately into sweat patches, nor the patch drug concentrations that might be expected from any such transfers. Thus, the study only demonstrates that drugs can be found in the post-mortem skin and adipose tissues of apparent drug users. The study provides no experimental support for the authors' speculation about the possibility of such tissue stores of drug leading to subsequent positive sweat patch test results. In fact, the post-mortem tissue stores observed in this study could have actually reflected very recent drug use by the subjects, in which case any possible positive sweat patch result would be a true positive, correctly identifying the recent use of drugs. The study provided no experimental support for any postulated mechanism of any long-term storage of drugs whereby a drug user may have a positive sweat patch test result weeks or longer after drug use.

In fact, studies on drugs in skin tissues have demonstrated that the skin is not a long-term reservoir for drugs. Studies of regular drug users who enter a locked ward for research studies on the sweat patch and have sweat patches applied upon entry have demonstrated that negative sweat patches are obtained shortly after cessation of regular drug use, generally within one week or so. In other studies, after controlled acute drug dosing and associated sweat patch testing, it has been demonstrated that most of the administered drug which is detected in sweat is eliminated within the first one to two days after such dosing.

The Appendix authors claimed that this study showed that drugs are stored for long periods of time in adipose tissue and skin. In fact, the study was a post-mortem study and the study authors made no demonstration of how long the detected drugs had in fact remained in the skin from any supposed long-term storage, or whether the detection of drugs actually reflected recent ante-mortem drug use. Again, the study authors only speculated about the possibility of long-term storage of drugs in adipose and tissue stores which could possibly migrate outward through the skin to possibly result in positive sweat patches. Again, this was a post-mortem study. No living subjects wore sweat patches nor were there any living subjects who had documented prior drug use and were subsequently patched and had positive sweat patch results. The

study only demonstrated post-mortem detection of drugs in tissues and then simply speculated about the possibility of positive sweat patch test results from any supposed long-term drug reservoirs.

The Appendix authors claim that these results cast "crippling doubt on PharmChem's core biological assumptions". This study cannot be construed to demonstrate anything that realistically impugns positive sweat patch test results in living subjects.

The Appendix authors make the claim that this single study contradicts any claim that sweat patch testing has reached a level of general acceptance in the scientific community. A single study cannot be taken to reflect the views of the scientific community absent a polling of the relevant scientific community. The fact that many research centers around the world and by far the vast majority of publications on the sweat patch find the patch to be an accurate and reliable device certainly contradicts the Appendix authors' claim about the patch lacking scientific acceptance.

After review of some of the same studies cited by the Appendix authors, SAMHSA indicated in 2004 in the Federal Register "Also, scientific advances in the use of head hair, sweat, and oral fluid in detecting drugs have made it possible for these specimens to be used in federal programs with the same level of confidence that has been applied to the use of urine." SAMHSA, Federal Register, 4/13/04, 69 FR 19689.

• PharmChem's Internal Studies

The Appendix authors comment on supposed internal studies performed by PharmChem staff but also note that these supposed studies were never published. This is a key point in attempting to give any scientifically valid weight to these supposed internal studies. The Appendix authors refer to observations made by Dr. Fred Smith, who apparently had obtained and reviewed internal laboratory test result documents from PharmChem. Dr. Smith claims that these documents represent studies actually performed by PharmChem and their associated test results. I have also received and reviewed what I believe are the same documents reviewed by Dr. Smith and I find them of little persuasive scientific value. The documents consist of almost 700 pages of GC/MS chromatograms (almost exclusively for amphetamine and methamphetamine), along with only a few typed sheets and hand-written notes, almost all of those undated and unsigned. These documents contain no clear documentation that specifically and unambiguously connects the numerous chromatograms to any particular study, nor are there any clearly documented conclusions about what the results may purport to show. Dr. Smith claims to be able to make sense of these documents, and that they demonstrate what experiments were done and what the results of those experiments were. In contrast, my review of these documents does not allow for any such firm conclusions about what experiments were in fact actually performed, and what the specific test results were for the supposed experiments. There is nothing in these documents whereby a scientist or other party has clearly summarized or indicated what experiments were in fact performed, what results were obtained for specific experiments, and any conclusions about what the results demonstrate. In my view, these documents are incomplete and ambiguous and therefore carry little scientifically valid weight.

Appendix Authors' Summary of Scientific Evidence

The Appendix authors again cite results from "real life" studies indicating false positive sweat patch results for supposed drug abstinent individuals. But, as noted above, none of the real-life studies actually proved that the individuals with the claimed false positive sweat patches were in fact completely abstinent. The criteria used for assumed abstinence were "negative" urine test results. But the urine testing as performed in these studies was not sufficiently frequent nor sufficiently sensitive (including effectively measuring the extent of urine dilution) to definitively identify any occasion drug use.

The Appendix authors also point out that speculation by experts cannot displace the results of scientific research, without identifying any particular experts they claim are speculating. I note that one of the articles the Appendix authors have relied upon, the Levisky skin study, in fact does exactly what the Appendix authors find unacceptable. Levisky et al. simply speculate that the potential for drugs found in post-mortem skin and adipose tissue may be a basis for subsequent positive sweat patch test results. These authors are simply speculating about that possibility, but somehow the Appendix authors seem to find that speculation acceptable.

The Appendix authors conclude by indicating that these studies are the best that science has to offer. But that does not mean that conclusions can reach beyond what the studies actually demonstrated.

Additional References Cited

Included in their reviews of the above six bulleted references, the Appendix authors cited an additional three references.

• D. Kidwell et al., Cocaine Detection in a University Population by Hair Analysis and Skin Swab Testing, For. Sci. Int., 84, 75 (1997)

• D. Kidwell et al., Testing for Drugs of Abuse in Saliva and Sweat, J. Chrom. B, 713, 111 (1998).

• J. Sellers et al., Effect of shampoo on cocaine uptake in hair, TIAFT–SOFT Conference, 1994, Abstract #188 (oral presentation).

D. Kidwell et al., Cocaine Detection in a University Population by Hair Analysis and Skin Swab Testing, For. Sci. Int., 84, 75 (1997)

This study was cited by the Appendix authors when indicating that isopropanol cleaning does not remove all drug residue from the skin and that drug residue can remain on an individual's skin for several days.

The cited study in part involved adding cocaine or its metabolite benzoylecgonine (BE) in isopropanol to subjects' skin (importantly, there was no indication if the skin was pre-cleaned as in other of these authors' studies) and then swabbing the skin with isopropanol wipes after various periods of time and hygiene practices. No sweat patches were applied and tested as part of the study. When small (20 ng) amounts of cocaine or BE in isopropanol solution were applied to skin and then the skin swabbed, recovery of cocaine was less than 100% and declined rapidly within ¼ to ½ hr after application. The authors indicated that the loss was possibly due to absorption. But there was no demonstration that if the applied drug was absorbed into the skin, that it remained therein so as to be subsequently detectable in a sweat patch. When larger amounts of cocaine or BE (10 µg) in isopropanol solution were applied to skin, cocaine was detectable in the isopropanol swab up to 65 hr, but the amount detected was only 3 ng/swab. Had this entire 3 ng amount of cocaine been incorporated into a sweat patch, the test result would have been reported negative (requiring 25 ng cocaine/patch for a positive test result). The same would be true for the 5 ng detected at 41 hours. Thus, this study only demonstrated that when cocaine in isopropanol solution is applied to skin it may be detectable in subsequent isopropanol skin swabs up to 65 hr thereafter but the swab detectable amounts were not sufficient for positive sweat patch test results. Again, there was no demonstration that if the applied drug was absorbed into the skin, that it remained therein so as to be subsequently detectable in a sweat patch.

D. Kidwell et al., Testing for Drugs of Abuse in Saliva and Sweat, J. Chrom. B, 713, 111 (1998).

This review article was cited by the Appendix authors when indicating that isopropanol cleaning does not remove all drug residue from the skin and that drug residue can remain on an individual's skin for several days.

This review article cited the results from the above study (D. Kidwell et al., Cocaine Detection in a University Population by Hair Analysis and Skin Swab Testing, For. Sci. Int., 84, 75 (1997). The authors indicated that the cited study demonstrated that drugs could be detectable up to three days after application to the skin. But the study never demonstrated that any such residual drug could lead to a subsequent positive sweat patch result. The study showed that even after applying 10 µg of cocaine in solution to skin, after 41 or 65 hours less than 5 ng of drug remained removable by isopropanol swabs, which if completely transferred to a subsequently applied sweat patch would be an amount insufficient to report a positive test result. The study never demonstrated that any of the applied drug could reside within the dermal layers so as to be subsequently detected in a sweat patch. Thus, the authors have only speculated about the possibility of any such residual drug leading to subsequent positive sweat patch test results. This is the same speculation that the Appendix authors have indicated cannot displace the results of actual scientific research.

J. Sellers et al., Effect of shampoo on cocaine uptake in hair, TIAFT–SOFT Conference, 1994, Abstract #188 (oral presentation).

The cited abstract (for a 15-minute oral presentation) indicated that 12 commercially available shampoos were included in the study but the pH of the shampoos was not specified in the abstract. It is possible that the pH of the shampoos was provided during the presentation, but the cited abstract alone provides no support for the Appendix authors' statement regarding "…material with a pH greater than seven, such as many common soaps and shampoos". Furthermore, the results of this study do not appear to have been published in the peer-reviewed literature.

I have above provided my summary comments about the studies cited in the Appendix A. I am prepared to address in further detail any of the cited studies as may be needed or to respond to any questions you may have.

Dr. Leo Kadehjian