CONCISE SUMMARY

HCM exposure studies have been of immense significance considering the exposure possibilities through the occupation and ambient environment. The criteria for industrial/ municipal/ hospital discharges/ waste have been based on toxicological profile of individual chemicals. In present scenarios where the exposure to pollutant is almost always heterogeneous, the investigations undertaken are of significance. Since the pollutants pave their way to the humans through the bioaccumulation and biomagnifications with in different components of the environment the exposure level to several of the toxicants is generally at very low doses but for prolonged period of time. During such a long exposure period various classes of organicals do get metabolized and get excreted while metals may accumulate with in various target and nontarget organs, therefore, to mimic such exposure situation it was decided to select both the organicals and metals as test chemicals.

The blood urine and tissue samples for toxicant analysis were collected only on or just prior to autopsy and no intermittent collections were made. The organicals, phthalate acid dibutyl ester and dichlorobenzene have very short half life and therefore quite low levels were detected in the blood and tissues, however, the wide range of the metabolites was detected in the urine samples of high dose exposed animals. The metals were detected at both the doses on 60 and 120 days. Therefore it is inferred that:

1. The toxicants administered are present in the animal body/ fluid/ tissues during the exposure and/ recovery phases.
2. All the administered parent compounds accumulated in all the tissues studied, while metabolites of organicals were detected in urine, particularly in high dose treated group. This is suggestive of normal toxicological manifestations describing systemic distribution, tissue accumulation, biotransformation and excretion mechanisms.
3. Since, the experiments are conducted under standard laboratory conditions the toxic responses are the actual responses due to administration of HCM at dosed comparable to NOAEL.

The literature evidenced induction of oxidative stress by administered toxicants individually and findings of present experiments exhibited the same in all the tissue studied when toxicants are administered as HCM at NOAEL doses for sub chronic duration. Therefore it is inferred that:

1 The toxicants distributed and accumulated at various levels in different tissues pose direct effect on the functioning of the cell of these tissues.
2 The variable oxidative stress response is suggestive of differences of accumulation pattern and content as well as susceptibility of the tissues to the toxicants administered.

The indicators of liver function tests are expressed in serum under the pathological conditions of liver. In present findings the structural damage to hepatocytes is correlated with cellular metabolic alterations as well as serum parameters. Therefore it is inferred as

1 The alterations in the serum indicators of liver function test are actually due to loss of structural and functional integrity to various cell of liver; these were reversible by day 120.
2 The loss of structural integrity and cell specific changes are correlated with the bioaccumulation in liver of administered toxicants.

The kidney functions are compartmentalized into various sections of renal tubule. It is represented overall in kidney function test assessed as serum parameters. On the basis of finding it is inferred as:

1 Structural damage to glomeruli including the podocytes and mesangial cells indicate damage to filtration apparatus and the function.
2 Segments specific variations in the structural integrity and damage are reflected as parameter specific variation suggestive of multisite effect of the toxicants on kidney leading to overall effect on functions.

3 The loss of structural integrity and cell specific changes are correlated with the bioaccumulation in kidney of administered toxicants at doses comparable to NOAEL.

It is expected that the parent organicals and their metabolites may accumulate in liver and the adipose tissues. Low level of these compounds especially in liver is suggestive of their rapid biotransformation and excretion leading to clearance from the body. Among the two organicals only dibutyl phthalate ester was detected in testis and epididymis following 60 day exposure. On the other hand the administered metals Cd and Cr potentially accumulate in testis and epididymis. Therefore it is inferred that:

1 The effect on testis and epididymis is largely due to the metals and the contribution of organicals in causing direct toxic effect in these tissues would be less.

In testis the Sertoli cell and spermatogenic cells exhibit variations in their susceptibility and toxic responses at different stage of development or progression of spermatogenesis. The variations observed in toxic effect at different seminiferous SE stages hence corroborate with the structural functional mechanisms of the testis. The spermatogenic cells undergo both mitotic and meiotic division and hence, SE stage specific studies are extremely relevant. It is inferred from the studies that:

1 The SE stage IX to XIV are more sensitive than stage I to VIiI and the overall sensitivity is graded as higher in SE stages XII to XIII> IX to XI> XIV> I to IV> V to VI> VII to VIII.

2 The cells at late stages of 1st meiotic division are more sensitive to toxicant action than the cells at undergoing 2nd meiotic division.

3 The sperm head anomalies are induced during early metamorphic stages as round spermatid and therefore elongating spermatids were structurally abnormal. However, if the structural anomaly was not significantly induced till the early

elongation phase such spermatids successfully completed metamorphosis and appeared normal.

4 The Sertoli-Sertoli junctional complex functioning as blood-testis-barrier is also damaged and therefore significant changes are noted in the crypt and adluminal regions of SE.

5 The early loss of more mature spermatogenic cells through sloughing and Sertoli cell cytoplasmic blebbing are indicative of structural and functional damages to the Sertoli spermatogenic junctional complexes and to the Sertoli cell cytoskeleton.

6 The loss of spermatogenic cells may not be extensive at both the doses and durations however, variations in the frequency of occurrence of tubules at different SE stages strongly suggests spermatogenic impairment that may lead to increase the duration of one spermatogenesis cycle.

7 The alterations in the steroidogenesis biosynthetic mechanism and serum testosterone levels indicate significance on steroidogenesis which may be a direct action on the Leydig cells or mediated through the hypothalamo-hypophysial-gondal axis (the effect on hormonal axis has been well documented for the toxicants individually).

8 The alteration in epididymal function confirmed toxicity induction at the accessory organs level also.

9 The spermatozoa's structural and functional changes confirmed that HCM exposure at NOAEL for subchronic duration does potentially impair fertility of the experimental animal (although mating studies are essential to conclude about fertility potential however present finding are sufficiently suggestive).